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Editorial

Thrombolytic therapy

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The successful development of a practical form of therapy designed for the rapid dissolution of thrombi, recently formed in the vascular bed, would represent a major therapeutic advance. No one would welcome more the virtues of such a therapeutic advance than the cardiologist, who daily observes the ravages of the thrombotic complications of atheromatous disease of the coronary vessels. The recent introduction into clinical medicine of thrombolytic preparations for the treatment of peripheral and pulmonary thromboemboli suggests that clot-dissolving agents may soon be recommended for the treatment of acute coronary thrombosis and myocardial infarction; if so, then it behooves us to examine carefully the current status of thrombolytic therapy.

Thrombolytic therapy is based on the principle that clots can be dissolved enzymatically in vivo provided that the circulating plasma is endowed with an increased clot-dissolving or thrombolytic activity for adequate periods of time; evidence supporting this principle has been obtained repeatedly both from in vitro and in vivo studies.[1] In animals, unequivocal evidence has been obtained that systemic thrombolytic states of the requisite degree successfully mediate the dissolution of experimentally induced thrombi,[2,3] and similar observations now have been made in man. Thus, the initial objective in thrombolytic therapy is to impart and sustain in the circulating plasma a powerful clot-lysing ability; thrombolytic agents represent the means by which such enhanced thrombolytic or clot-dissolving activity can be induced, controlled, and maintained in the patient.

Unfortunately, considerable controversy exists among investigators as to whether the desired therapeutic thrombolytic state can be more readily and more safely achieved by substances, such as streptokinase or urokinase, which activate the naturally occurring but normally quiescent fibrinolytic enzyme system,[5] or by the direct use of plasmin,[6] the proteolytic enzyme which ultimately is involved in the natural resolution of fibrin. The biochemical and pharmacologic basis for this controversy is more complex than the simple choice of agents which, in vitro, may produce similar effects; the interested reader should consult recent articles which deal with this aspect of the problem.[7-9] Regardless of this fundamental controversy, the principle concerning the induction and maintenance of a measurable, regulated thrombolytic state in the circulating plasma is in no way circumvented by the nature

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of the agent used for thrombolytic therapy.

The two thrombolytic preparations available commercially, Actase and Thrombolysin, though both designated by their manufacturers as human fibrinolysin (plasmin) are, on analysis, mixtures of streptokinase (a bacterial activator derived from hemolytic streptococci) and plasmin (the proteolytic enzyme derived from human plasma). However, the thrombolytic activity they induce in plasma (in vivo and in vitro) can be traced to their streptokinase content.[10,11]

Different problems are posed by each of the two preparations. Actase contains relatively small amounts of both streptokinase and plasmin.[10,11] In vitro evidence suggests that the infusion of 1-2 vials of this preparation into man, as advised, could hardly be expected to exert any detectable effects since the circulating plasma contains sufficient antiplasmin and antistreptokinase (all adult plasma contains large amounts of antiplasmin, and, consequent to previous streptococcal infections, significant but variable amounts of antistreptokinase) to inactivate rapidly the recommended dose of this agent. The prediction that this agent, in the recommended doses, would fail to raise plasma thrombolytic activity in vivo has been confirmed by direct experimental trials in man.[10,12]

In contrast, Thrombolysin contains considerably more streptokinase and plasmin per vial.[11] Though the antiplasmin activity of the circulating plasma is still readily sufficient to inactivate all the plasmin present, there is sufficient streptokinase in this preparation, when used in the recommended dose of 4 or more vials per day, to induce an active thrombolytic state in some patients, comparable to that which would have been induced by streptokinase alone. Since Thrombolysin is best viewed as a streptokinase preparation containing added plasmin, its proper use for instituting a reproducible thrombolytic state should be governed by the same considerations which apply for streptokinase alone, where patient dosage (based on a dose prediction test) must be *individualized*, depending upon the amount of circulating antistreptokinase.[4,13] The fixed or standard dosage schedule currently recommended for Thrombolysin makes it impossible to insure that the patient will develop an active thrombolytic state, and the lack of laboratory controls makes it impossible to determine what type of thrombolytic state is being evaluated therapeutically. For this reason, it is essential that the haphazard nature of the enzymatic state induced in patients with this agent be replaced by a well-regulated one before studies are undertaken to determine its clinical efficacy in the treatment of disease.

Serious problems also have arisen concerning the standardization of the commerically available streptokinase-plasmin mixtures. These mixtures are currently standardized in terms of arbitrary fibrinolytic units, and each manufacturer has his own. The need for appropriate standardization is emphasized by the fact that a vial of Actase of 50,000 fibrinolytic units contains less than one-quarter the streptokinase unitage and one-twentieth the plasmin unitage of a vial of Thrombolysin, also described as containing 50,000 fibrinolytic units.[11] Furthermore, the fibrinolytic assay employed fails to distinguish between the relative concentration of the two components, each of which is handled entirely differently in vivo. Intelligent use of these preparations requires that the content of their individual components be known.

Some of the other, as yet, unsolved problems of thrombolytic therapy can be illustrated by a consideration of the application of this type of treatment to coronary heart disease. Progress in this development has been recently reviewed,[14,15] and the magnitude of the problem as regards clinical evaluation discussed. However, any trial with thrombolytic therapy, if it is to be meaningful, must evaluate a controlled thrombolytic state, not just the administration of a particular agent with a variable response in patients. Thus, decisions must be made concerning the nature and duration of the thrombolytic state to be evaluated and the laboratory controls to be used in guiding therapy. These laboratory controls, to be most practical, must be simple ones, a matter of particular importance if the results indicate that the therapy may be recommended for general clinical use. With the streptokinase system (which is applicable to the currently available commercial prepara-

tions), simple tests are available for predicting dosage, and the induced (occasionally hazardous) coagulation disorder may be monitored by serial antithrombin times. Still needed is a simple, reliable, quick test for adequately following plasma thrombolytic activity.

Finally, it has been our conviction that thrombolytic agents should not be used in extensive clinical trials until they are virtually free of pyrogenic activity. Although the incidence of such reactions has, in general, steadily decreased with increasing purity of the preparations, the problem of eliminating or preventing this undesirable feature has not been solved completely. Febrile reactions prevent the maintenance of adequate thrombolytic therapy and, in critically ill patients, may provoke a fatal outcome. In acute myocardial infarction, where thrombolytic therapy, under optimal circumstances, only can hope to benefit a moderate number of patients, i.e., those with underlying thrombi and salvable myocardium,[16] the over-all beneficial effects could be virtually eliminated by a relatively small but significant incidence of severe pyrogenic reactions. Though some investigators have found it expedient to limit thrombolytic therapy to a 4-hour period so as to minimize the problem of pyrogenicity, experimental observations suggest that such expediency may well eliminate the major portion of the therapeutic benefit, since, under controlled conditions, long periods of treatment are often necessary to effect and sustain the complete dissolution of a thrombus.[4,17] Because pyrogenic reactions jeopardize both the therapy and the patient, it would seem wisest to concentrate on eliminating the cause of such reactions.

The current emphasis on practical trials with thrombolytic agents, rather than the further development of scientific principles, is a matter of considerable concern. Obviously there is a compelling need for practical trial, once the science and pharmacology of a desired thrombolytic state induced by a particular agent is sufficiently established, but the encouragement of practical trial in lieu of the establishment of sound principles is not sensible. The argument raised in favor of practical trials, before the establishment of therapeutic principles, is that the effect in patients is paramount; therefore, if an effect is apparent, other considerations are relatively of little importance. Such a view may have virtue in the treatment of diseases in which the natural course is well defined and predictable, such as certain malignant or infectious diseases. However, the application of scientific method to the evaluation of an agent in the treatment of diseases with extremely variable symptomatic, morbidity, and mortality patterns, such as the thromboembolic disorders, is the most difficult in the entire area of clinical investigation, and an empirical clinical evaluation, in trials based on inadequately controlled or limited studies, defies critical analysis.

One cannot expect resolution of the confusion surrounding the current state of thrombolytic therapy until such basic problems as the choice of agents, simple laboratory guides for instituting and controlling therapy, proper standardization of agents, elimination of pyrogenic contaminants, etc., are solved sufficiently to allow for the establishment of sound pharmacologic principles in the development of thrombolytic therapy. The inherent potential with this form of therapy is so great, and preliminary human observations sufficiently promising, that major encouragement should be directed toward the solution of these fundamental problems, both by laboratory investigation and carefully planned trials which correlate clinical and laboratory measurements. Conversely, we must recognize that we are insufficiently advanced in the development of scientific principles to encourage clinical trials under any except clinical investigative circumstances. Only with the establishment of a firm foundation will this new and exciting field of therapeutics develop soundly at the clinical level.

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Clinical communications

Endocardial fibroelastosis

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The term *endocardial fibroelastosis* was introduced by Weinberg and Himelfarb[1] in 1943, to describe a cardiac condition of obscure etiology in infancy, in which the most striking feature was diffuse left ventricular endocardial thickening. As a term it has proved to be the most widely used among the many which have been applied to similar cases.

It has since been the practice to include under this term all kinds of endocardial thickening in infancy and early childhood, and, in addition, to refer to morphologically similar cases seen in European and North American adolescents and adults as *endocardial fibroelastosis* of these age groups.[2-5] The assumption is often made that these adult cases are in some way connected with the infantile condition, but this is open to question. Moreover, the correctness of the term *endocardial fibroelastosis*, even as it is applied in infancy, is also questionable, since it is descriptive only of the endocardial condition and does not indicate any other cardiac anomaly which may, and often does, accompany the endocardial thickening. Further, and more important, it implies that the endocardial lesion is the primary one, whereas there is a great deal of evidence to the contrary.

The pattern of endocardial fibroelastosis

The condition is characterized by a diffuse fibroelastic thickening of the endocardium (Fig. 1) which in the majority of cases is confined to the chambers on the left side, particularly the left ventricle. The right ventricular endocardium may in a few cases be thickened, but the degree and severity of the change is not comparable with that seen on the left. In about half of the reported cases some other cardiac condition was also found, the most common being aortic stenosis. The condition is found in early infancy, and, as a rule, death occurs between the age of 3 and 12 months, and it may be sudden. There is no significant sex variation; it is found in both white and Negro children; and there are several reports of it occurring in twins and siblings.[6]

Until recently, all hearts which showed diffuse endocardial thickening have been considered as a single group, but when a large number of cases are reviewed, they fall naturally into two main categories: (1) those cases in which the endocardial thickening is accompanied by some other gross cardiac anomaly, and (2) those in which the mural endocardial thickening appears to be the only lesion of significance. In the first category, the most common concomitant conditions, by far, are aortic and mitral stenosis, particularly the former. Others may occur, but none with any frequency—for example, premature closure of the foramen ovale,[7] an adult type of coarctation of the aorta, ventricular septal defects,[8] and the triad of aortic atresia, hypoplasia of the aorta, and rudimentary left ventricle.[9] Often included with these is the syndrome of anomalous left coronary artery, but this should be

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Fig. *1.* The diffuse fibroelastic endocardial thickening from a case of endocardial fibroelastosis without valvular disease. Weigert's elastica, ×90.

regarded as a separate condition, although diffuse left ventricular endocardial thickening is present in all examples.

Cases in the second category are perhaps less common, but of more interest. Here no other lesion apart from the endocardial thickening is apparent, and this circumstance has in the past caused confusion, since it was often argued that, if the mural endocardial lesion could occur alone, the valvular lesions seen in the other group were not essential and due only to an extension of the mural process. Thus, the possibility that two groups were present, linked only by endocardial thickening, was seldom considered.

The etiology of endocardial fibroelastosis

In the past a variety of theories have been put forward to account for the endocardial thickening, with or without valvular disease. The earliest theory was that the lesions were the result of a fetal endocarditis, but it has been shown[10] that this assumption had no evidence to support it. Others[11-15] believed that the lesion was a congenital cardiac anomaly arising probably from the overgrowth of connective tissue to involve both valves and mural endocardium. The source of this has never been determined and the embryologic arguments advanced are unconvincing, particularly when an explanation of the group of cases without valvular disease is attempted.

Johnson[7] proposed that in all cases of endocardial fibroelastosis the cause was anoxia of the endocardium. This he suggested was due to a deficient coronary blood supply which resulted from either aortic stenosis or an anomalous left coronary artery, or defects in the perforation or closure of the foramen ovale. This hypothesis has received some support,[9,16,17] but it has several defects. First, it seems particularly difficult to render the endocardium anoxic since it receives its main supply of blood directly from the ventricle. Secondly, there is no evidence that anoxia per se produces endocardial thickening, and third, the hypothesis does not explain the group of cases with no demonstrable defects other than left ventricular endocardial thickening.

The anoxic theory has been challenged,[18] and it has been proposed that conditions predisposing to increased intracardiac pressure and dilatation are present in all cases, and that these mechanical factors produce a reactive diffuse endocardial thickening. This is in accordance with the views of earlier investigators.[19-21]

Recently, too, the distinction between the two groups already referred to has been made[8]; and the cause in this group without valvular disease has been considered to be, almost by exclusion, some defect in cardiac muscle which is not morphologically obvious. Evidence is now forthcoming that this group may have a congenital defect of cardiac muscle, termed *myocardial hyperplasia*.[22] This state is defined as one in which the cardiac fibrils remain at their immediately prenatal size and do not increase in size, as is seen in hearts with valvular disease and also in normal growth. It has also been suggested that in this group of cases there is an inborn enzymatic defect which acts on the cardiac muscle.[23] The connection between "hyperplasia" and this enzymatic defect is not yet clear.

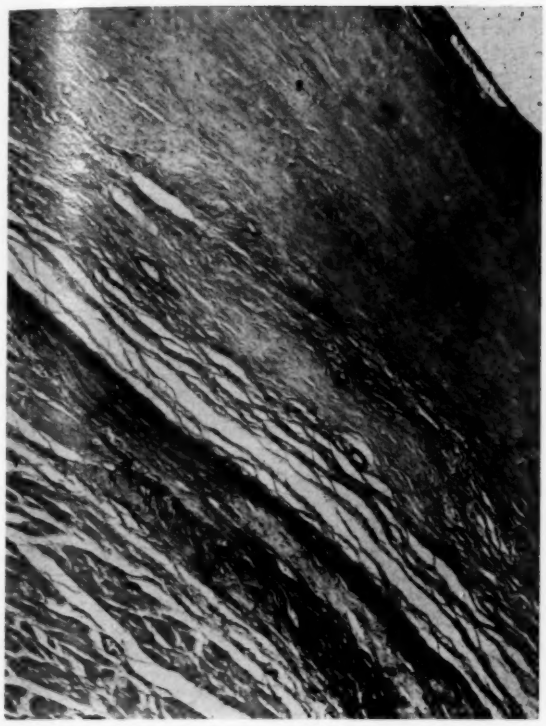

Fig. 2. Endomyocardial fibrosis (Uganda). The superficial areas of the endocardium are composed of mural thrombus and hyaline material. Hematoxylin and eosin, ×130.

With regard to the connection between endocardial thickening and increased intracardiac pressure and dilatation, there are several adult states in which this sequence appears to be present—for example, in the left auricle in association with mitral stenosis,[24] as a sequelae of left ventricular dilatation for a variety of reasons,[25] and a similar type of endocardial thickening is seen in the dilated left ventricle of adolescents who die from pseudo-hypertrophic muscular dystrophy.[26]

In most examples of diffuse endocardial thickening in infancy, circumstances exist which produce either increased intracardiac pressure or dilatation, or both—for example, aortic stenosis, the massive myocardial fibrosis in anomalous left coronary artery, and congenital "hyperplasia" of cardiac muscle. Thus, as far as it goes, the hypothesis is satisfactory, but discrepancies exist; for example, cardiomegaly occurs without endocardial thickening, and not all valvular diseases in infancy or, for that matter, in adults are complicated by diffuse endocardial thickening.

The pathogenesis of the endocardial thickening

Little attention has been paid to the processes which thicken the endocardium in cases of endocardial fibroelastosis. Theoretically, there are three ways by which the result may be brought about: (1) by the deposition and incorporation of mural deposits, (2) by an overgrowth of connective tissue, and (3) by replacement fibrosis.

In the common types of adult endocardial thickening, particularly in African endomyocardial fibrosis (Fig. 2), in myocardial infarction (Fig. 3), and in mural rheumatic endocarditis (Fig. 4), the thickening is, in some measure, due to the deposition and incorporation of mural thrombi, and this will eventually lead to fibroelastic thickening of the endocardium similar to that of endocardial fibroelastosis (Fig. 5).

If the endocardium in the infant condition is examined with these mural deposits in mind, it will be found that they occur with some frequency (Figs. 6 and 7). Besides the more obvious recent surface deposits, there are other appearances which suggest that similar processes have occurred

Fig. 3. Myocardial infarction. Organizing mural thrombus overlying an area of myocardial infarction.

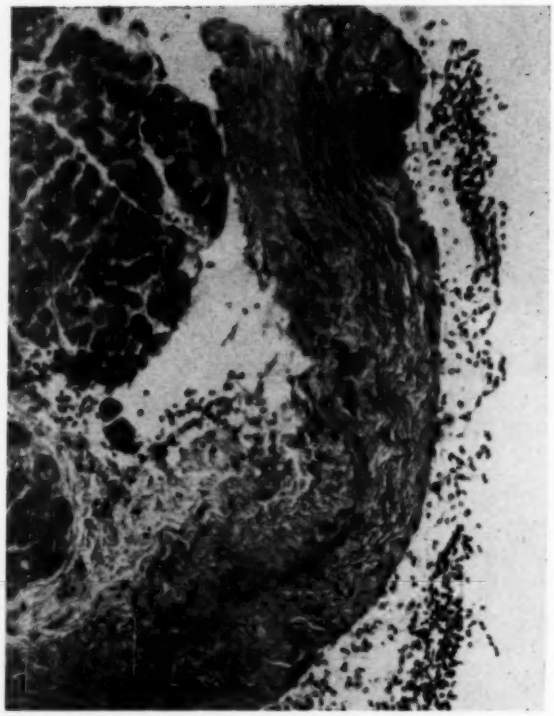

Fig. 4. Rheumatic endocarditis. A biopsy specimen showing two small mural deposits being incorporated. Hematoxylin and eosin, ×130.

in the past. For example, quite often the intratrabecular clefts in the left ventricle are filled with loose vascular connective tissue, so that they are wholly or partly obliterated, and, at times, material which stains as fibrin can be found in this tissue (Figs. 8 and 9). This process, aided by the intraventricular pressure, tends to flatten and smooth the surface of the left ventricle, producing the characteristic gross appearance. A further example of surface activity is seen in other areas in which the endocardium has a vascular, almost granulation-tissue appearance, with small tags of fibrin adhering to it (Fig. 10), and, in addition, in many areas the superficial layers are of a spongy loose texture (Fig. 11), suggestive of fairly recent formation.

It has further been shown[28,29] that when these surface layers of the endocardium are examined by the electron microscope, they are found to contain fibrin which is not apparent in contiguous histologic sections. This would seem to indicate that the deposition and incorporation of fibrin are more widespread than the histologic appearances would suggest, and therefore more important in the pathogenesis of the thickening than at first seems likely.

To most observers, however, the endocardial thickening has been taken as some type of hyperplasia—either a reaction to anoxia or to increased strain. It is true that the endocardium, for the most part, looks as though the normal tissue elements have been multiplied some tenfold, but there is no method by which we can judge the extent or degree of the hyperplasia, and it must be borne in mind that a similar type of endocardial thickening can be produced largely by the organization of mural thrombi.

Some degree of subendocardial fibrosis and replacement fibrosis of the subjacent myocardium are common features of endocardial fibroelastosis, but the severity of these changes vary widely. It does seem likely, however, that they are more conspicuous in hearts with valvular stenosis.[12] These processes are not, in fact, part of the endocardial thickening, although it is difficult to separate the layers when fibrosis is extensive, and it is likely that, for the most part, this distinction has not been made.

Fig. 5. Myocardial infarction. Fibroelastic thickening of the endocardium overlying a healed infarct. Weigert's elastica, ×100.

Fig. *6*. Endocardial fibroelastosis. Recent, but organizing, thrombotic deposit in the left ventricle. Hematoxylin and eosin, ×100.

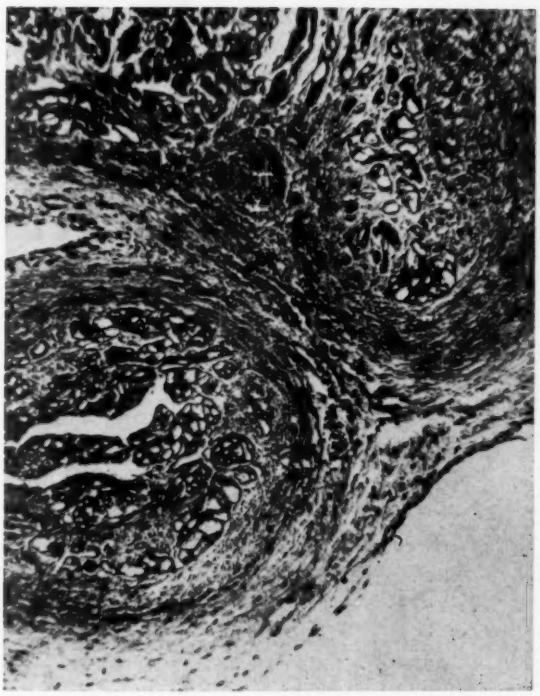

Fig. *8*. Endocardial fibroelastosis. An intratrabecular cleft partly obliterated by vascular connective tissue. Hematoxylin and eosin, ×110.

Fig. *7*. Endocardial fibroelastosis. Small deposits of fibrin in an intratrabecular cleft. Hematoxylin and eosin, ×180.

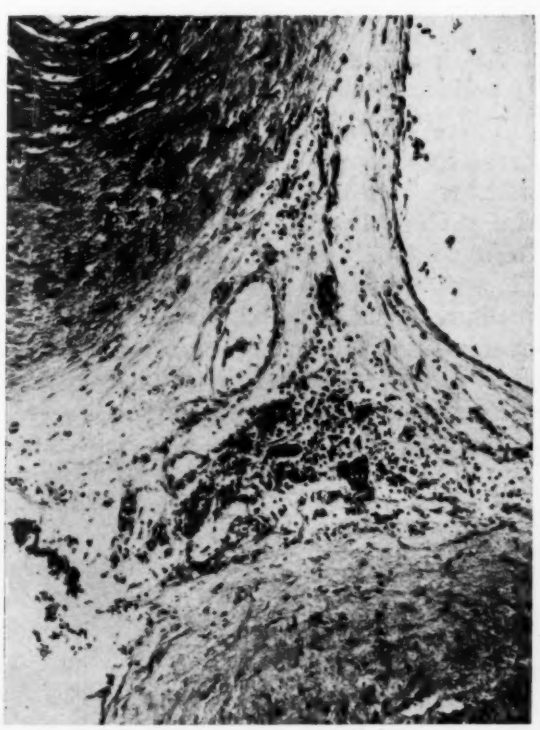

Fig. *9*. Endocardial fibroelastosis. Trabeculae joined by loose vascular connective tissue which contains fibrin. Hematoxylin and eosin, ×120.

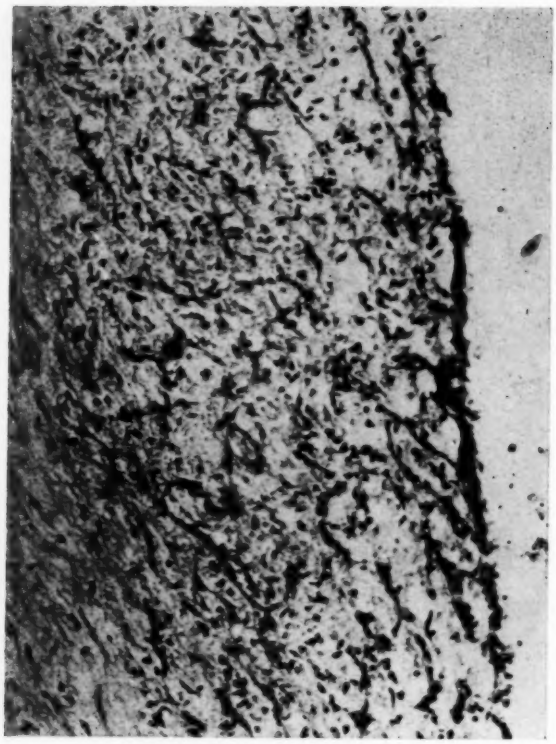

Fig. *10.* Endocardial fibroelastosis. An area of the endocardial surface with the appearance of granulation tissue. Hematoxylin and eosin, ×180.

Adult and adolescent endocardial thickening

There are numerous reports on endocardial thickening in adults, and a lesser number of reports on adolescents, in which the etiology is obscure. The tendency has been to label those cases as *endocardial fibroelastosis*; some workers have been inclined to the view that they are surviving examples of infantile endocardial fibroelastosis,[2,3,5] whereas others have regarded the endocardial thickening here as a nonspecific reaction to a number of different underlying cardiac conditions.[4] At present the cases are too heterogeneous for any real order to emerge, if order does in fact exist. No connecting factors have been found between these scattered European and North American cases, with the more well-defined African type of endocardial thickening known as *endomyocardial fibrosis*,[10] on one hand, and the infantile endocardial fibroelastosis, on the other.

With regard to the connection with the infantile condition, there are several points of difference. First, the adult and adolescent cases seldom, if ever, show the diffuse type of endocardial thickening characteristic of the infantile group; thickening in the adult and adolescent tends to be more patchy. Secondly, the degree of myocardial fibrosis is much greater in the adult and adolescent cases. This latter has been dismissed as an effect of the long-standing endocardial thickening, but the evidence from other types of endocardial thickening suggests that this sequence is dubious, and that it is the presence of the myocardial fibrosis which is probably of primary importance. It should be noted, also, that the adult and adolescent thickening is always much more obviously due to the incorporation of mural thrombi and fibrin deposits than to the infantile type of thickening.[4] Furthermore, the histories of the adult and adolescent cases suggest that the first episode of cardiac failure was of sudden, or relatively sudden, onset after apparent good health, a history somewhat inconsistent with their having possessed since infancy a progressive variety of infantile endocardial fibroelastosis.

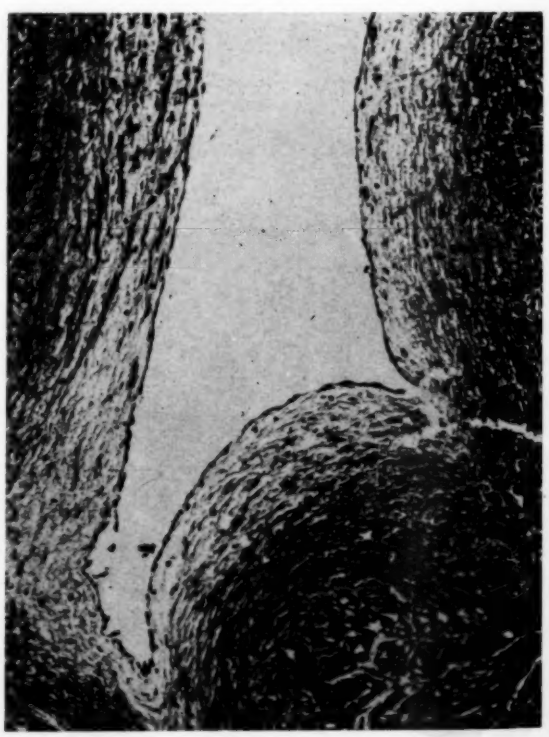

Fig. *11.* Endocardial fibroelastosis. The surface layer is spongy in texture and contains little elastic tissue. Hematoxylin and eosin, ×150.

Conclusions

It seems likely that the condition which at present we call *endocardial fibroelastosis* is a disease of infancy, and, moreover, can be divided into two distinct groups. In one group, severe independent lesions are present, particularly aortic stenosis, and these appear to be the factor of primary importance, with the diffuse endocardial thickening as one of the effects of the lesion on the related chamber. In the second group, the mural thickening is not accompanied by other gross cardiac defects but may be related to a congenital hyperplasia of cardiac muscle, and may again be only a sequelae to the cardiac dilatation which ensues from this state. The term *endocardial fibroelastosis* is not suitable, therefore, for either group, since in neither is the endocardial lesion the primary change.

Summary

The etiology and pathogenesis of so-called endocardial fibroelastosis is reviewed in the light of recent information. It is suggested that the endocardial lesion is secondary to increased intraventricular pressure and dilatation caused by some other cardiac anomaly, and that the incorporation of surface deposits of fibrin play a part in the pathogenesis of this endocardial thickening.

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Perinatal changes in the pulmonary vascular bed with stenosis and atresia of the pulmonic valve

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Certain congenital cardiac anomalies lead to extensive anatomic and physiologic alterations in the pulmonary arterial bed. These have usually been noted when the lesser circulation has been subjected to increased pressure and volume of blood flow.[1] The possibility exists that adaptive changes may also develop in the pulmonary arteries when pressures and flow are abnormally reduced. Such a reduction may occur when the pulmonic valve is narrowed or closed. In the present report, congenital pulmonic stenosis and atresia are shown to lead to an abnormal fetal development of the pulmonary arterial bed which is often continued after birth. We are unaware of any previous reports of such an abnormal development.

Subjects

Fifteen infants with pulmonic stenosis who died during the perinatal period were studied. Two were stillborn; the rest varied in age from 24 hours to 16 weeks. Stenosis was severe in all cases. The ductus arteriosus was anatomically closed in all who were over 3 weeks of age. In one infant (1 day old) the ductus arteriosus was apparently closed at birth. In most instances the pulmonary artery was described as being hypoplastic. Seven of the infants had tetralogy of Fallot. Over-all cardiac enlargement was described in many instances. Both in infants with tetralogy and in infants with isolated pulmonic stenosis the right atria were noted to be dilated. In 10 of these infants the right ventricle was described as being abnormally thick walled.

In all of the infants, cyanosis was noted at or soon after birth. Early respiratory distress was noted in about one half. Five were reported to be weak and lethargic in the days after birth. Of those who survived for a time, most had feeding problems and gained weight poorly. Five were found to have a cardiac systolic murmur. Two who survived for several weeks developed polycythemia. Thoracic x-ray films revealed a reduced pulmonary vascular pattern as well as an enlarged heart in 3 infants. Peripheral edema and congestive hepatic enlargement were noted in 4.

Also studied were 21 infants with pulmonic valvular atresia who were stillborn or lived less than 16 weeks after birth. Hypoplasia of the pulmonary arteries was described in 10, and 5 had only atretic cords where the pulmonary artery is usually found. In 6 infants the only blood supply for the lungs was through the bronchial

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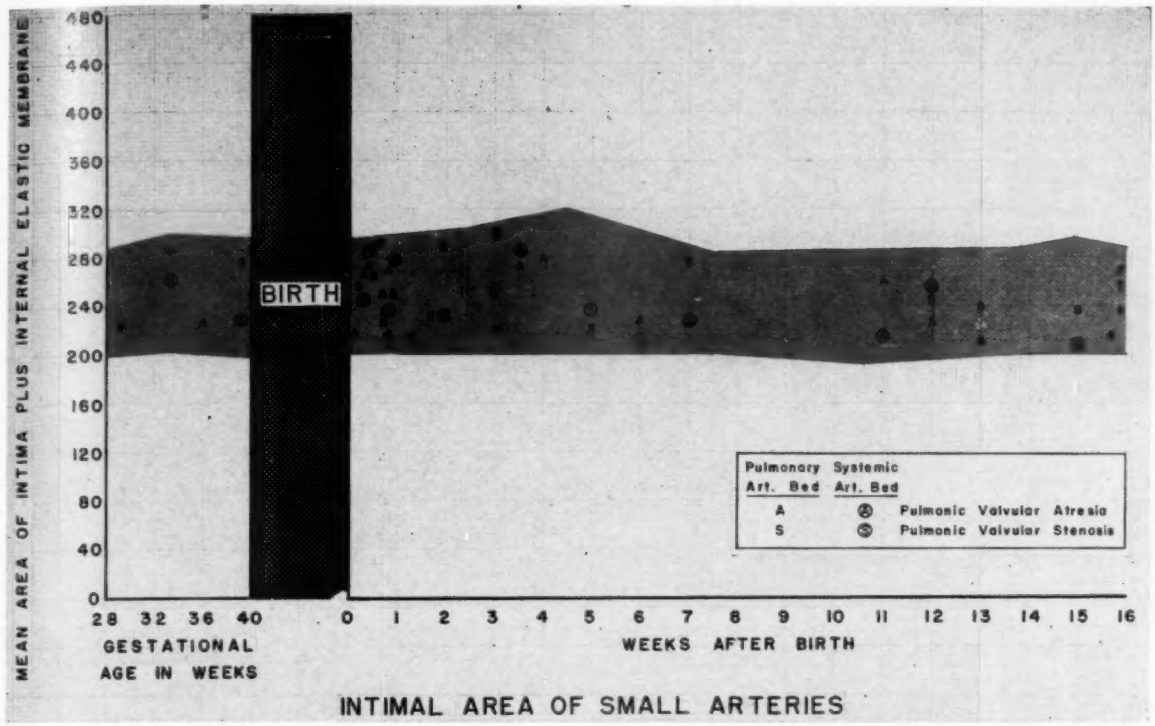

Fig. *1.* The mean areas of intima combined with internal elastic membrane for small arteries from patients with pulmonic valvular atresia and stenosis. The areas in which normal values are found are lightly shaded. Normal values have been published previously.[2]

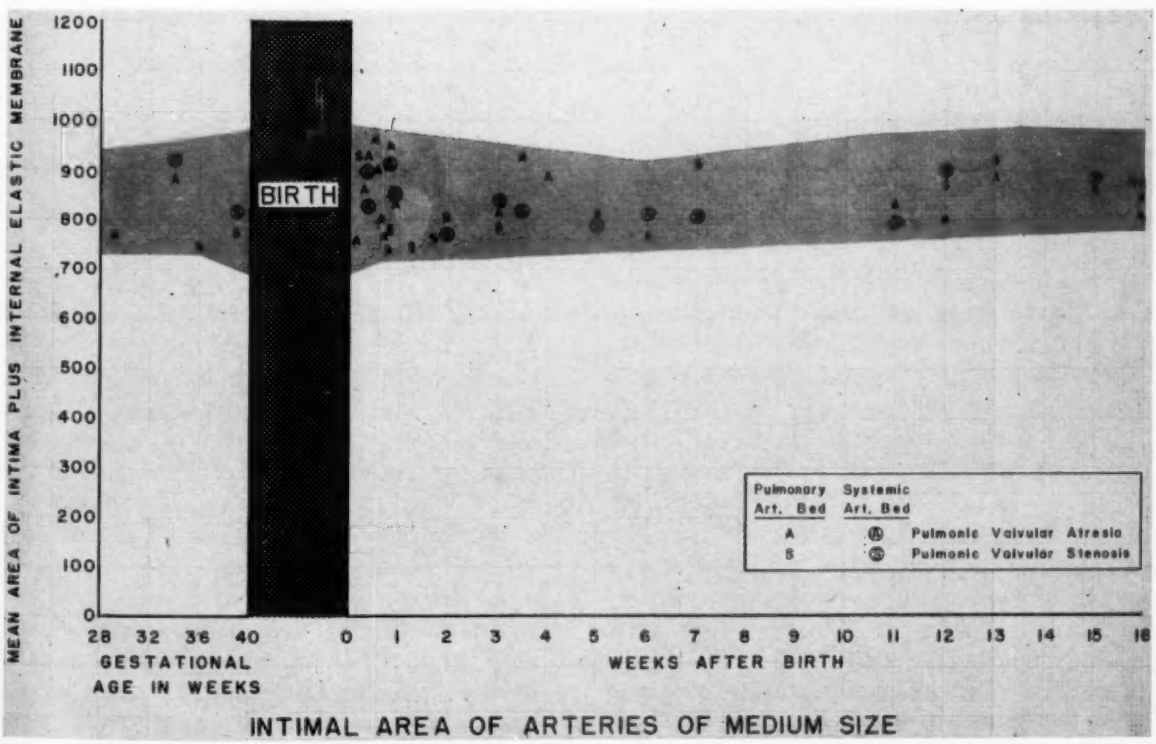

Fig. *2.* Same as Fig. 1, except that values are for medium-sized arteries.

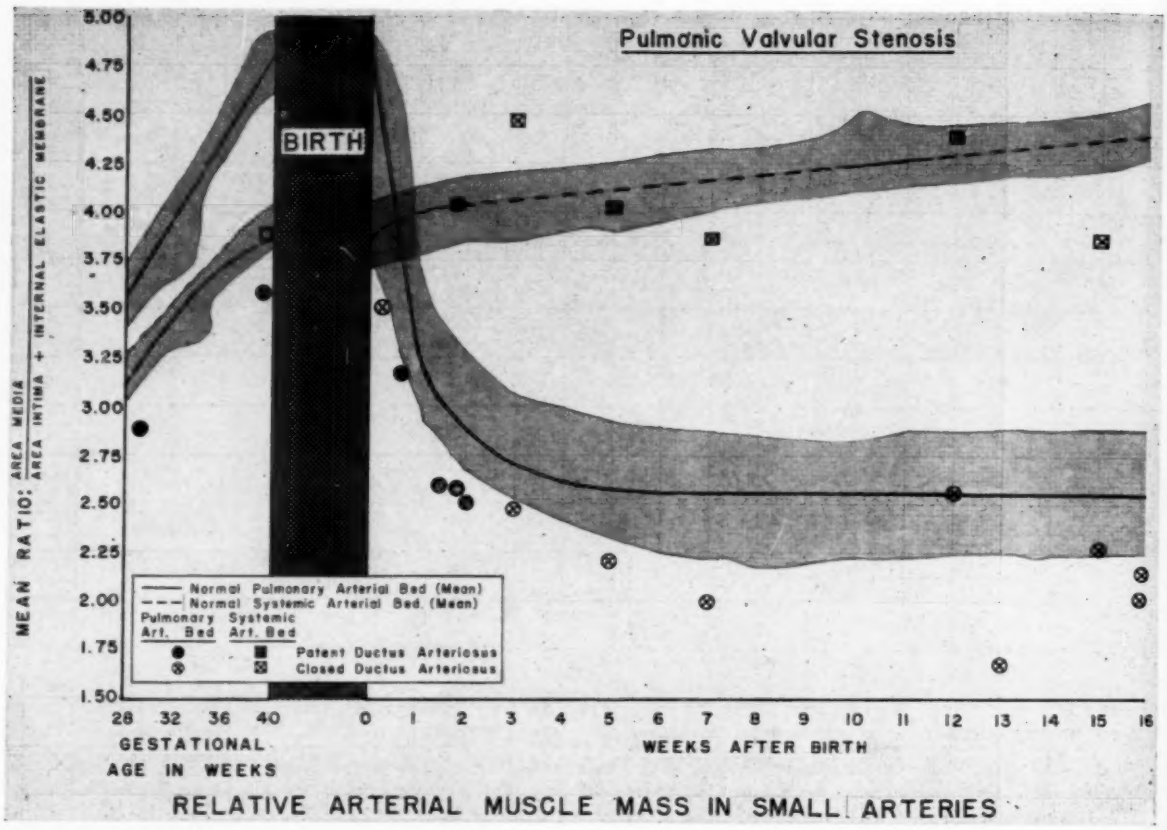

Fig. 3. A ratio reflecting arterial muscle mass for small arteries from patients with pulmonic valvular stenosis. The areas in which normal values are found are lightly shaded. These normal values have been published previously.[2]

arterial system. In the other 15 infants the blood reached the pulmonary circuit through a patent ductus arteriosus. In 3 of these latter cases the ductus was abnormally patent, the infant being more than 3 weeks of age. None of the infants had transposition of the great vessels. One infant (age 23 days) had biatrium triloculare. Some type of interatrial septal defect permitting right-to-left interatrial shunt was found in all cases.

The clinical histories of the infants with pulmonic valvular atresia were similar to those of patients with severe pulmonic stenosis. Liveborn infants were noted to be cyanotic at an early stage, and 3 who survived for more than a month became polycythemic. Weakness, lethargy, and poor feeding were described in 8. A systolic, precordial murmur was detected at some time before death in all but 5 of the liveborn infants. X-ray evidence of cardiac enlargement and a reduction of the pulmonary vascular bed were also described in 5 infants. Progressive, congestive hepatic enlargement was common before death.

Methods

Previously described methods were used to measure arterial changes in both circulations.[2] In each case, multiple blocks of pulmonary tissue, selected at random, were sectioned at 6 microns and stained with Verhoeff and van Gieson stains. Similar sections were prepared from one or more blocks of pancreas in about one half of the cases. With the aid of a camera lucida and a planimeter, the relative cross-sectional areas of lumen, intima, and media of small muscular arteries and arterioles were determined. In each vessel the internal elastic membrane was arbitrarily included as part of the intima. Sections from cases under study and sections from controls were thoroughly mixed and examined in a random manner to avoid bias.

Results

Initially, the mean area of intima combined with internal elastic membrane for vessels in each case was charted against the stage of development (Figs. 1 and 2). These were compared with previously published values for normal controls.[2] The values proved to be relatively similar and constant throughout the period of study for both normal controls and for patients with pulmonic stenosis and atresia. Therefore, the relative areas of these structures were selected as a convenient reference base line to which the arterial medial mass could be compared. As in the previous study,[2] a numerical expression:

$$\frac{\text{area arterial or arteriolar media}}{\text{area intima + internal elastic membrane}}$$

was adopted as a relative measure of arterial muscle mass. In each case this value was determined for 15 to 30 arterioles and small arteries in the pulmonary circulation, with luminal diameters between 5 and 30 microns. A similar number of arteries with luminal diameters between 30 and 50 microns were also measured. In those cases in which tissue was available, measurements were also recorded for the systemic circulation. These two categories of small vessels were selected because they presumably make a major contribution to vascular resistance.

In patients with pulmonic stenosis, vessels of the systemic arterial bed were found to be normal. The arteries and arterioles were well developed, and examination of the ratio

$$\frac{\text{area media}}{\text{area intima + internal elastic membrane}}$$

showed that the medial muscle coat of these vessels was normal in area (Figs. 3 and 4). Values for normal controls have been published previously.[2] In contrast, abnormalities in medial mass were present in the pulmonary arterial bed. Both before and after birth, ratios were about 20 per

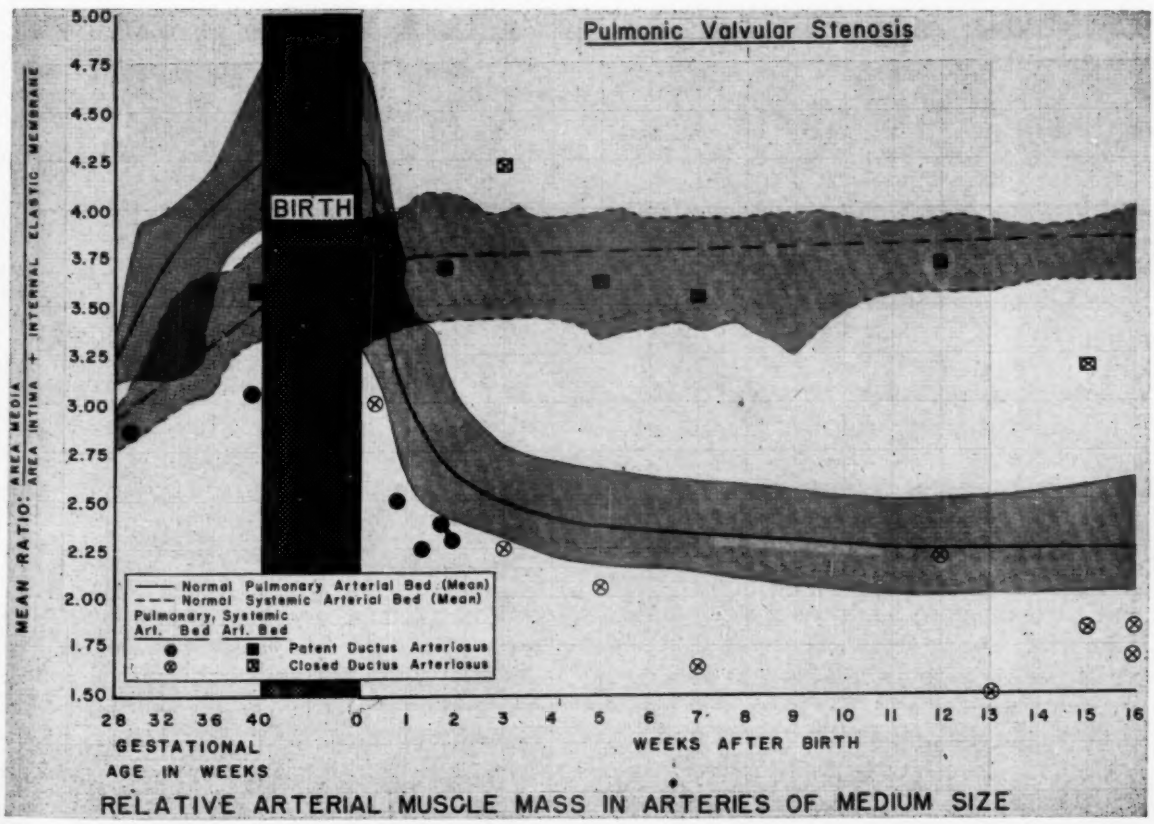

Fig. 4. A ratio reflecting arterial muscle mass for medium-sized arteries from patients with pulmonic valvular stenosis. Normal values are found within the lightly shaded areas.

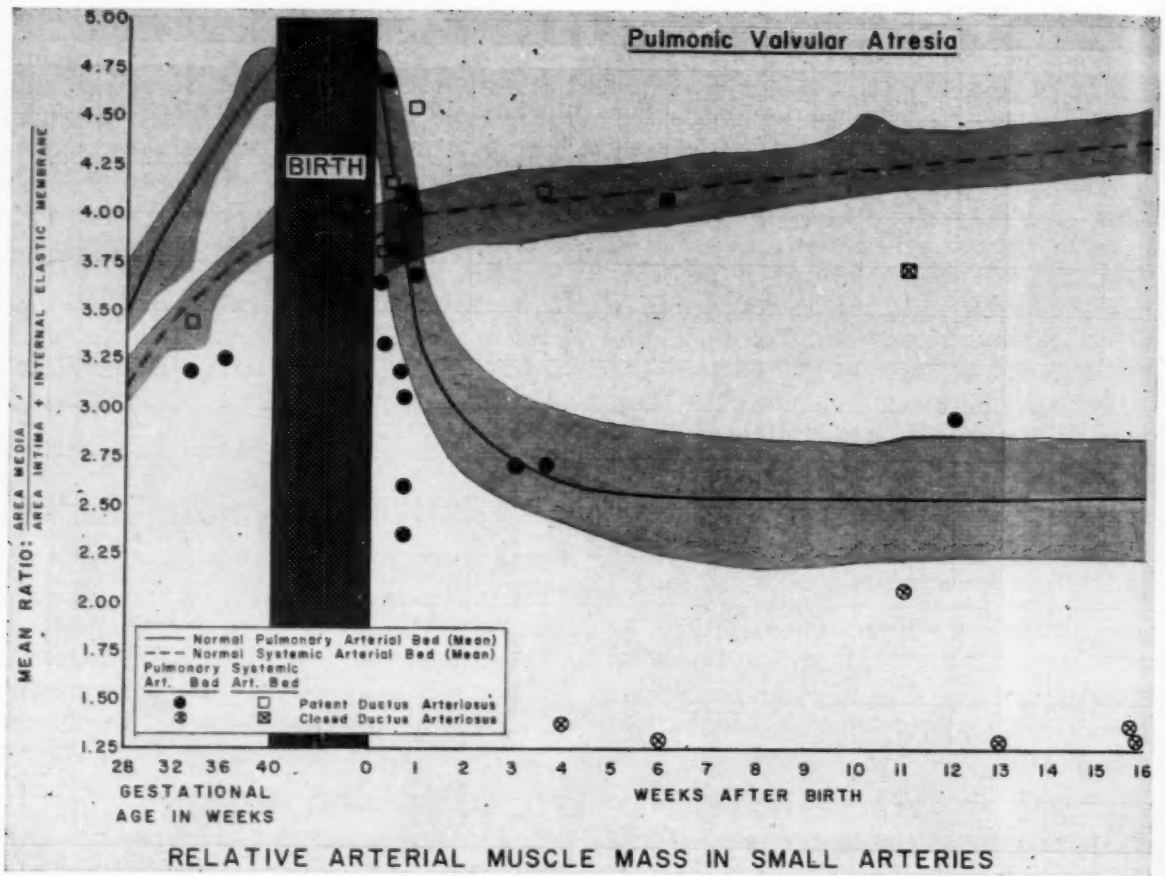

Fig. 5. A ratio reflecting arterial muscle mass for small arteries from patients with pulmonic valvular atresia. The areas in which normal values are found are lightly shaded.

cent smaller than those found in control cases (Figs. 3 and 4). This diminution in smooth muscle was found in arteries and arterioles of all sizes. Abnormalities of the intima or elastic membrane were absent, and the pulmonary veins and bronchial vessels were structurally normal.

Many of the findings in patients with pulmonic atresia were similar. The muscular coat about the systemic arterial bed developed normally, both before and after birth (Figs. 5 and 6). In contrast, the values for muscle about the pulmonary arterial bed before birth were considerably lower than the control values (Figs. 5 and 6). Of the 10 liveborn infants who survived for less than 1 week, 6 had values below those found in any of the control cases. None had values above those found in the control cases.

In those infants with atresia who survived for 3 weeks or longer, changes in the pulmonary arterial muscle mass seemed to be related to the patency of the ductus arteriosus. In the 6 infants in whom the ductus was closed the muscle mass was much reduced, being only about 50 per cent of control values. In the group of 3 in whom the ductus remained patent the muscle mass was not reduced, but remained at the level found in other infants with atresia at birth (Figs. 5 and 6). Abnormalities of the arterial intima and elastic membrane were absent in the entire group.

Discussion

The current study demonstrates that smooth muscle in the pulmonary arterial bed develops abnormally in some infants with pulmonic stenosis and atresia, both before and after birth. In a group of stillborn infants, this muscle mass was abnormally reduced. In fact, this mass was less than that found about comparable systemic arteries, a reversal of the normal pattern.[2] If arterial muscle mass is a reflec-

tion of intra-arterial pressure in such cases, fetal pressures in the greater circulation may have been above those in the lesser circuit. Such pressures might have permitted a left-to-right shunt through the ductus arteriosus, a reversal of the normal direction of flow. This postulate obviously needs clinical confirmation.

After birth, evolution of the pulmonary arterial muscle mass could be correlated with the state of the ductus arteriosus. In patients with pulmonic atresia and a closed ductus arteriosus the relative pulmonary arterial muscle mass was at very low levels. In such cases the very low pressures in the lesser circulation after birth probably permitted a relative rapid reduction in the pulmonary arterial muscle mass. When the ductus closed normally in cases of pulmonic stenosis, the relative muscle mass decreased at a normal rate even though it was already at a low level at birth. The resultant subnormal level of this muscle mass throughout the neonatal period probably reflected the low pulmonary arterial pressures which exist in such cases.[3] In contrast, when the ductus remained patent (in cases of pulmonic atresia), the muscle did not decrease, but rather maintained itself at the birth level throughout the period of study. This was no doubt related to the fact that the lesser circulation was subjected to high systemic pressures.[1] Such high pulmonary arterial pressures have been reported in cases with pulmonic stenosis and a patent ductus.[4]

In contrast to these findings, Dammann and Ferencz[5] have reported that the postnatal pulmonary arterial muscle mass is normal in patients with pulmonic stenosis and atresia. Several factors may explain this apparent discrepancy. In contrast to their conclusions in 4 of their youngest patients, their data show that the relative pulmonary arterial muscle mass was at less than normal levels.[5] Also pertinent is the fact that most of their patients were older than were those in the current study. If higher pulmonary arterial pressures and blood flow made this longer survival pos-

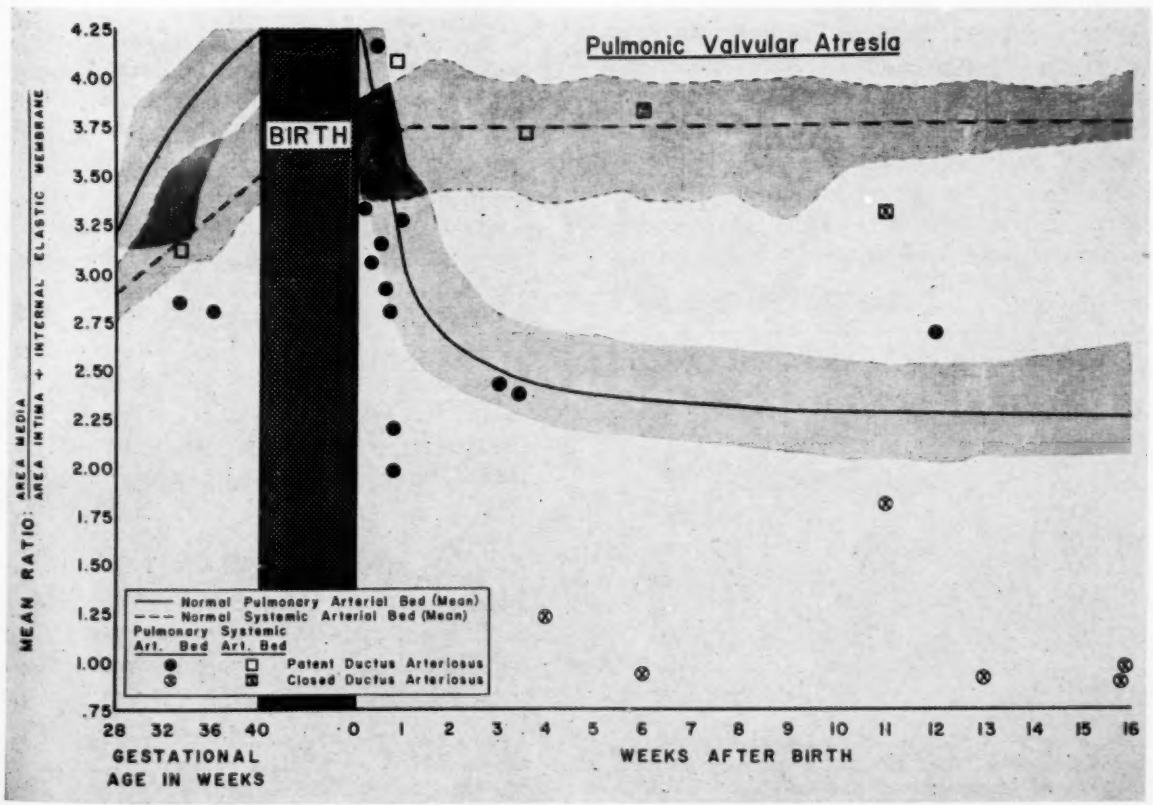

Fig. 6. A ratio reflecting arterial muscle mass for medium-sized arteries from patients with pulmonic valvular atresia. Normal values are found within the lightly shaded areas.

sible, a more nearly normal pulmonary arterial muscle mass would be expected. In our cases, cyanosis suggested that pressures and flow were very low.[3] Lastly, Dammann and Ferencz's data may have been subjected to distortion by arterial dilatation or contraction. This is inherent in a method which compares thickness of the arterial wall to diameter of the lumen of the artery. The method used to measure arterial muscle mass in the current study was probably not influenced by such dilatation and contraction. In a previous experimental study it was shown that dilatation of pulmonary arteries had no influence on the ratio used to measure arterial mass in the current study.[2]

Summary

The perinatal development of muscle in the pulmonary arteries is influenced by reductions in pressure and flow through these vessels. Before birth there is a moderate reduction in the pulmonary arterial muscle mass in cases of both pulmonic stenosis and pulmonic atresia. This reduction continues after birth in many cases of pulmonic stenosis. In cases of pulmonic atresia in which the ductus arteriosus is closed the pulmonary arterial muscle mass is markedly decreased. In cases in which the ductus remains patent the muscle mass does not decrease, but is maintained. The implications of these findings are discussed.

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Pathology of the conduction system in acquired heart disease
Complete right bundle branch block

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The anatomic substrate of the electrocardiographic abnormality complete right bundle branch block in acquired heart disease has been a subject of discussion for many years. The literature on this subject has been reviewed by Lenègre[1] and Lev.[2,3] According to Lenègre,[1] significant lesions in the right bundle branch are found in this electrocardiographic abnormality.

The present work is part of a long-term project wherein the purpose is to ascertain the anatomic substrate of disturbances in conduction in general. Previous work dealt with severe atrioventricular block[4] and masquerading bundle branch block.[5] The present study was made on 8 cases of coronary disease, and 1 of chronic myocarditis with abscesses; shortly before death in all of these patients the electrocardiograms showed a pattern of complete right bundle branch block.

Materials and methods

All electrocardiograms were obtained with the Sanborn Viso-Cardiette and included the standard and augmented unipolar limb leads and 7 precordial leads (Leads V_{3R} and V_1 to V_6). The diagnosis of a complete right bundle branch block was based on a QRS prolongation to 0.12 second or more and the presence of a slurred or notched R wave or rSR′ complex in the right precordial leads. Right ventricular hypertrophy was diagnosed when in the latter leads the QRS was entirely upright (R or rR′) or, in the presence of an S wave, the R′ measured 10 mm. or more.[6,7] The presence of left ventricular hypertrophy was assumed when the left-sided precordial

Table I. *Technical details*

	Case		*Number of sections*
1.	(A– 7–55)	R.G.	986
2.	(A– 87–56)	S.S.	961
3.	(A– 52–56)	R.G.	936
4.	(A–125–55)	H.R.	1,047
5.	(A–109–55)	M.K.	1,737
6.	(A– 41–55)	H.M.	918
7.	(A–175–55)	S.L.	864
8.	(A– 95–55)	M.O.	862
9.	(A–182–55)	G.S.	1,113

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Table II. *Anatomic findings in nine cases of complete RBBB*

RBB	Case 1		Case 2		Case 3		Case 4	
	a	*c*	*a*	*c*	*a*	*c*	*a*	*c*
S-A node	−	+	±	−	+	−	−	−
Approaches to S-A node	±	+	2+	+	4+	−	±	3+
Right atrium	±	−	2+	±	3+	−	±	3+
Left atrium	±	−	2+	−	+	−	−	+
Approaches to A-V node	±	−	+	±	2+	−	−	−
A-V node	−	+	−	±	±	−	−	±
A-V bundle, penetrating	−	−	−	±	±	−	+	+
A-V bundle, branching	±	+	+	+	±	−	2+	2+
RBB	2+	3+	3+	3+	3+	2+	2+	3+
LBB	±	±	3+	+	3+	−	3+	−
Left ventricle, anterior	±	3+	2+	2+	+	−	±	3+
Left ventricle, posterior	±	2+	2+	2+	+	−	±	2-3+
Right ventricle, anterior	−	−	+	−	+	−	−	1-2+
Right ventricle, posterior	±	±	2+	−	+	−	−	2-3+
Atrial septum	−	−	2+	−	±	−	−	+
Ventricular septum, anterior	±	2+	2+	+	+	−	+	2+
Ventricular septum, posterior	+	3+	2+	+	+	−	2+	2+
LV-H	2+		+		+		3+	
RV-H	+		2+		+		2+	
Ramus ostii cavae superioris	−		−		−		4+	
Ramus septi fibrosi	+		±		−		2+	
Arteries and arterioles of septum	2+		4+		2+		−	

a: Acute pathologic change.
c: Subacute and chronic pathologic change.

Table III. *Correlation of anatomic and electrocardiographic data with regard to right-sided or*

Case	*Anatomy*										
	Hypertrophy		*Infarction or fibrosis*				*Bundle branch lesion*				*QRS duration*
							Right		*Left*		
	Right	*Left*	*R*	*L-A*	*L-P*	*Septal*	*Old*	*Recent*	*Old*	*Recent*	
1.	+	2+	−	3+	2+	2+	3+	2+	±	±	0.12
2.	2+	+	+	2+	2+	+	3+	3+	+	3+	0.12
3.	+	+	− (Myocarditis)			−	2+	3+	−	3+	0.12
4.	2+	3+	2+	3+	3+	3+	3+	2+	−	3+	0.12
5.	3+	4+	+	2+	2+	2+	4+	2+	+	3+	0.14
6.	2+	+	2+	+	+	+	4+	±	−	±	0.14
7.	±	±	−	+	+	+	±	2+	±	+	0.14
8.	4+	4+	+	3+	+	3+	+	3+	−	3+	0.16
9.	4+	4+	2+	4+	3+	+	2+	3+	+	3+	0.12 → 0.16

Table II.—*(Cont'd)*

RBB	Case 5		Case 6		Case 7		Case 8		Case 9	
	a	*c*	*a*	*c*	*a*	*c*	*a*	*c*	*a*	*c*
S-A node	+	−	−	−	−	−	−	−	2+	−
Approaches to S-A node	±	+	−	+	±	−	±	±	2+	2+
Right atrium	±	1-2+	−	+	±	−	+	−	4+	4+
Left atrium	−	−	−	+	−	−	3+	−	2+	−
Approaches to A-V node	±	+	−	+	−	−	−	−	+	−
A-V node	±	±	−	±	+	−	−	−	−	−
A-V bundle, penetrating	±	−	−	±	−	−	−	−	−	−
A-V bundle, branching	±	+	−	±	−	+	−	−	2+	2+
RBB	2+	4+	±	4+	2+	±	3+	+	3+	2+
LBB	2-3+	+	±	−	+	±	3+	−	3+	+
Left ventricle, anterior	±	2-3+	+	±	2+	+	3+	−	4+	4+
Left ventricle, posterior	+	2-3+	+	+	+	+	+	−	3+	3+
Right ventricle, anterior	−	+	+	2+	+	+	+	±	3+	+
Right ventricle, posterior	−	2+	+	2+	+	−	+	±	2+	3+
Atrial septum	−	+	−	+	−	−	2+	−	3+	−
Ventricular septum, anterior	2+	2-3+	−	+	2+	2+	3+	−	4+	4+
Ventricular septum, posterior	2+	2-3+	±	+	2+	+	4+	2+	4+	4+
LV-H	4+		+		±		4+		3+	
RV-H	3+		2+		±		4+		4+	
Ramus ostii cavae superioris	−		−		−		−		3+	
Ramus septi fibrosi	4+		−		2+		+		3+	
Arteries and arterioles of septum	−		−		3+		4+		2+	

a: Acute pathologic change.
c: Subacute and chronic pathologic change.

left-sided ventricular hypertrophy, infarction, and bundle branch lesions

QRS configuration in V_1	*Electrocardiogram*						*Correlation of*	
	Evidence of							
	Hypertrophy		*Infarction*			*Left-sided conduction defect*	*Hypertrophy*	*BB lesion*
	Right	*Left*	*Anterior*	*Posterior*	*Lateral*			
QR	?	−	+	?	−	−	Partial	Excellent
Notched R	+	−	?	?	?	−	Good	Partial
			(Subendocardial injury)					
rSR′	−	+	−	−	−	−	Partial	Excellent
Notched R	+	−	Injury	−	−	−	Partial	Partial
rR′	+	−	+	+	+	±	Partial	Excellent
Notched R	+	−	−	−	−	−	Good	Excellent
R	+	−	+	−	+	−	Partial	Good
Notched R	+	+	+	−	+	?	Excellent	Partial
rS → Notched R	− → +	+ → −	−	+	−	+	Good	Partial

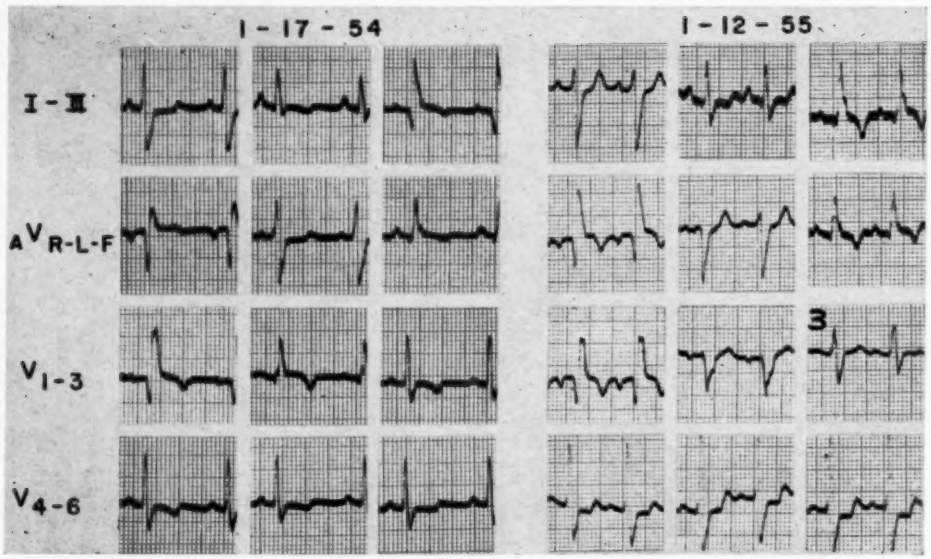

Fig. *1*. Electrocardiograms of Case 1. See text.

leads revealed a large R wave and/or a typical strain pattern of ST-T or a marked left axis deviation (to more than −30 degrees) was present in the frontal plane.[8] The diagnoses of recent and old myocardial infarction were based on conventional criteria.[9]

Each heart was examined in a manner previously described.[10] In this method a semiquantitative histopathological study of the entire heart is made, including the sinoatrial node, the approaches to the sinoatrial node, the atria, the approaches to the atrioventricular node, the atrioventricular node, the atrioventricular bundle, the bundle branches, the peripheral Purkinje network, and the entire ventricular myocardium. The number of sections studied in each case is given in Table I. The anatomic findings are presented in Table II. Anatomic findings referable to hypertrophy, recent or old bundle branch lesion, and recent or old myocardial infarction in the right and left ventricles are correlated with the electrocardiographic interpretation in Table III.

Report of cases

Case 1. (A-7-55) R. G.

CLINICAL DATA. This 62-year-old white woman with a history of diabetes mellitus for 10 years had several admissions to the Mount Sinai Hospital of Greater Miami: in 1949, for control of the diabetes; in 1953, for a kidney infection; in March, 1953, for myocardial infarction; and in January, 1953 and 1954, for episodes of acute pulmonary edema. The last admission was in January, 1955, for acute left hemiplegia and pulmonary edema. The blood pressure at this time was 210/110 mm. Hg, and the pulse rate was 120 per minute. The patient died 9 hours after admission.

ELECTROCARDIOGRAPHIC FINDINGS. An electrocardiogram on Jan. 7, 1954 (Fig. 1) revealed sinus rhythm, with a rate of 86, P-R of 0.16 second, and QRS of 0.12 second. QR complexes in the right precordial leads indicated the presence of a right bundle branch block in association with probable

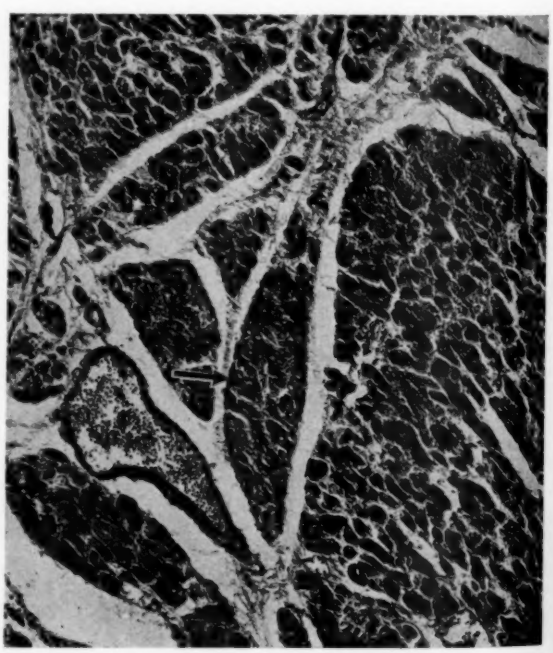

Fig. *2*. Case 1. Section through second portion of right bundle branch, showing fibrosis of about one third of its substance. Weigert–van Gieson stain, ×150.

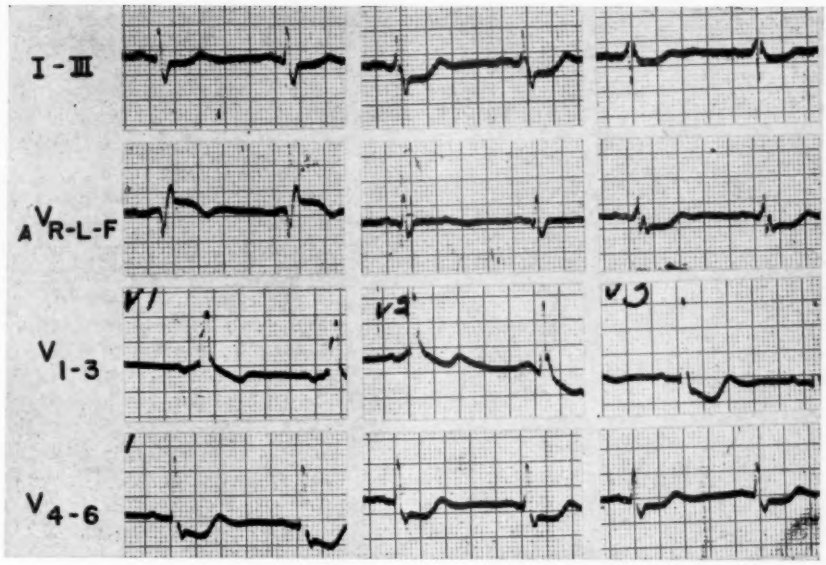

Fig. 3. Electrocardiogram of Case 2. See text.

old anteroseptal infarction. Small Q waves in Lead II and prominent ones in Leads III and aV_F suggested the possibility of an old posterior wall infarct. The abnormal ST-T contour was attributable in part to digitalis. In a record a year later (Jan. 12, 1955) (Fig. 1), at the time of the last admission, no substantial changes were noted except for a faster rate and less prominence of the alterations attributed previously to involvement of the posterior wall by the infarction.

POSTMORTEM EXAMINATION. Aside from the findings in the heart, the pathologic diagnoses were: (1) generalized arteriosclerosis and arteriolosclerosis; (2) intracerebral hemorrhage, severe; (3) bronchopneumonia, severe; and (4) pulmonary emphysema.

Heart: gross examination: The heart weighed 475 grams. Both ventricles were hypertrophied, the left more than the right. There was marked sclerosis of the coronary arteries, with narrowing in both the right circumflex and the anterior descending arteries. The posterior wall of the left ventricle was somewhat thinned and presented areas of scarification.

Heart: microscopic examination: *General pathologic change:* There was generalized arteriolosclerosis with acute and chronic organizing arteriolonecrosis, with accompanying inflammatory changes in the atria and ventricles, and acute epicarditis. *Left ventricle:* There was an old infarct involving the inner part of the anterior and posterior walls and extending into the papillary muscles. This was more marked in the apical half than in the basal half of the anterior wall and in the posterior wall. *Right ventricle:* There was slight fatty infiltration in the anterior wall, with slight fibrosis with a small scar in the posterior wall. *Ventricular septum:* A subendocardial scar involved most of the posterior septum, and the apical half of the anterior septum. In some areas this approached the right ventricular endocardium. There were also some small organizing infarcts at the base of the posterior septum. *Atria and atrial septum:* The findings were those of the generalized arteriolar necrosis and associated changes described previously.

Conduction system: *S-A node:* There was fibrosis and slight scar formation surrounding the artery of the node. In addition, there was a scattering of mononuclear cells within the node. *Approaches to the S-A node:* There were small scars in the atrial appendage adjacent to the wall, in addition to the vascular necrosis. *Approaches to the A-V node:* There was a slight infiltration of mononuclear cells, which was part of the vasculitis. *A-V node:* There was slight fibrosis and elastosis. *A-V bundle, penetrating:* There were no changes. *A-V bundle, branch-*

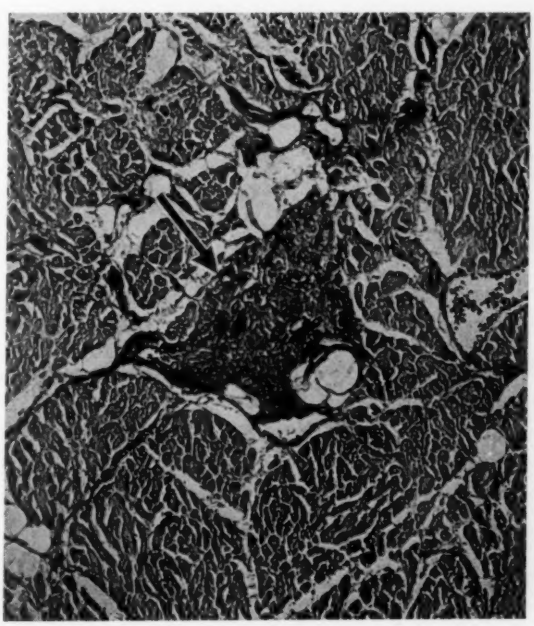

Fig. 4. Case 2. Section through second portion of right bundle branch, showing complete fibrosis and elastosis. Weigert–van Gieson stain, ×80.

Fig. 5. Case 2. Section through the beginning of the third portion of right bundle branch, showing acute necrosis of Purkinje fibers. Hematoxylin-eosin stain, ×60.

ing: There was slight fibrosis of the right side of the branching bundle, with mild acute degenerative changes. Scattered mononuclear cells were present at the bifurcation.

Right bundle branch: The first portion of the right bundle branch showed moderate fibrosis, about one fifth to one third of its substance being replaced by scar tissue. The second portion was similarly scarified, about one third to one half being replaced (Fig. 2). The third portion showed marked fibrosis with about three-fourths replacement. The moderator band was not present for analysis. In addition, there were foci of irregular staining of the right bundle branch throughout its course, with occasional infiltration of neutrophils and mononuclear cells.

Left bundle branch: The left bundle branch showed minimal focal fibrosis and occasional acute degenerative changes, with an infiltration of mononuclear cells at parts of the termination of the left bundle branch.

Blood supply to the conduction system: The ramus ostii cavae superioris showed no change. The ramus septi fibrosi showed moderate narrowing. There was moderate arteriolosclerosis and necrosis of the arteries and arterioles of the septum.

CARDIAC PATHOLOGIC DIAGNOSES. (1) Hypertensive, arteriosclerotic, and arteriolosclerotic heart disease, with severe narrowing of the anterior descending and right circumflex coronary arteries. (2) Old infarct of the septum and anterior and posterior walls of the left ventricle, with small microscopic zones of organizing infarcts in the posterior septum at the base. (3) Hypertrophy of the heart (left ventricle, moderate; right ventricle, slight). (4) Marked fibrosis of the right bundle branch. (5) Slight fibrosis of the sinoatrial and atrioventricular nodes and the branching portion of the bundle. (6) Acute generalized arteriolitis, with involvement of the myocardium, endocardium, epicardium, and the conduction system.

Case 2. (A-87-56) S.S.

CLINICAL DATA. This 68-year-old white man with a history of myocardial infarction 12 years prior to admission, and an uneventful course following this, was admitted to Mount Sinai Hospital on April 9, 1956. He complained of sudden onset of severe retrosternal pain which radiated to the left arm and was associated with profuse diaphoresis. On admission, he showed clinical evidence of shock, with a blood pressure of 90/60 mm. Hg and a pulse rate of 58 per minute. A few râles were noted at the lung bases, the heart sounds were distant, and no murmurs or rubs were detected. Subsequently, the blood pressure rose somewhat, but the patient experienced recurrent chest pain, lapsed into intractable shock, and expired 1 hour after admission.

ELECTROCARDIOGRAPHIC FINDINGS. The electrocardiogram (Fig. 3) showed a sinus bradycardia of 58, with a P-R interval of 0.18 second, and a QRS of 0.12 second. The contour of the P wave suggested atrial, predominantly left-sided, pathology, and that of the ventricular complexes, a right bundle branch block probably in association with right ventricular hypertrophy. There were no characteristic alterations attributable to a previous infarct, but there were features of acute coronary insufficiency with fresh subendocardial injury.

POSTMORTEM EXAMINATION. Aside from the findings in the heart, the pathologic diagnoses were: (1) generalized arteriosclerosis (a) aorta, (b) renal arteries; (2) pulmonary emphysema and fibrosis with chronic passive hyperemia; (3) fatty metamorphosis with peripheral fibrosis of the liver; (4) chronic splenic hyperplasia with fibrosis; (5) arteriolosclerosis of the kidney; and (6) hypertrophy of the prostate, slight.

Heart: gross examination: The heart weighed 320 grams. There was moderate hypertrophy of the right ventricle, with slight hypertrophy of the left. The coronary arteries showed severe sclerosis, with narrowing especially of the right main coronary artery. There was a brownish-red mushy thrombus 2 cm. from the mouth of the left coronary artery. There was a white scar, measuring 3 by 2 by 3 cm., involving the lateral portion of the posterior wall and the lateral wall of the left ventricle in its basal two thirds.

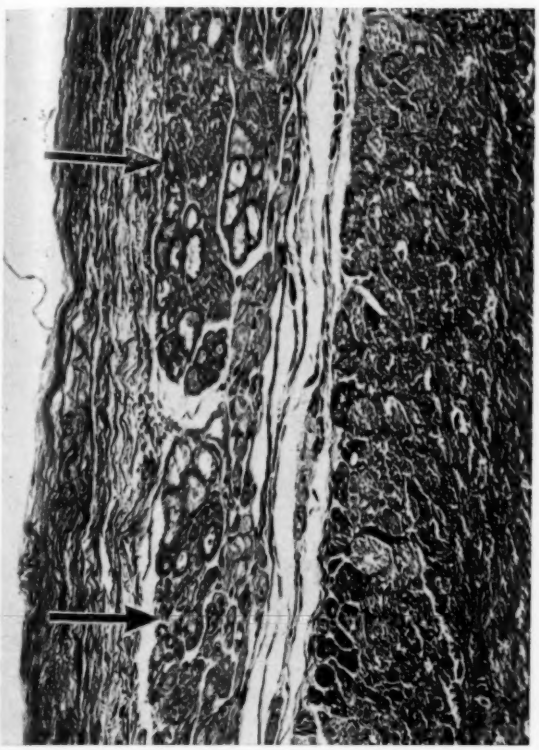

Fig. 6. Case 2. Section through upper part of left bundle branch, showing early necrotic changes. Hematoxylin-eosin stain, ×150.

Heart: microscopic examination: *General pathologic change:* There was generalized arteriolosclerosis and arteriolonecrosis. *Left ventricle:* There was a very recent infarct, with zones of organization involving all walls and the papillary muscles. In addition, there was an old scar in the lateral wall, extending into the lateral parts of the anterior and posterior walls. *Right ventricle:* The above-mentioned recent infarct extended into the anterior and posterior walls, more into the latter. *Ventricular septum:* The above-mentioned recent infarct involved both the anterior and posterior parts of the septum, with occasional small scar formation on the left side. *Atria and atrial septum:* These were involved in the recent infarct. The right atrium, in addition, showed occasional small zones of organization and some fibrosis.

Conduction system: *S-A node:* There was some irregularity in staining and considerable arteriolosclerosis. *Approaches to the S-A node:* There was a very recent infarct, with small zones of organization of the atrial appendage, with a small organizing mural thrombus. In addition, slight fibrosis of the atrial appendage and the posterior crest was present. Fibrosis in the superior approaches to the S-A node was evident. *Approaches to the A-V node:* There was slight fibrosis, with a very recent infarct. *A-V node:* Arteriolosclerosis of the node was apparent, with minimal degenerative changes. *A-V bundle, penetrating:* There was slight fibrosis in the distal portion. *A-V bundle, branching:* Slight fibrosis was present in the beginning. Small zones of acute degeneration and early necrosis were present which increased somewhat at the bifurcation.

Right bundle branch: Severe degenerative changes were present in the first portion, with slight fibrosis. In the second portion this fibrosis increased so that it replaced one third of the structure, and the branch became completely necrotic. The fibrosis then increased to about one half, and thereafter there was almost complete fibrosis and elastosis of the right bundle branch (Fig. 4), with necrotic changes in the remainder. Fatty infiltration appeared, with an infiltration of lymphoid cells. The fibrosis then diminished but the necrosis appeared to be complete, as the right bundle branch lay in the region of the early infarct of the septum. In the third portion the necrosis was marked (Fig. 5), and the fibrosis involved about one half of the bundle, accompanied by elastosis and fatty infiltration.

Left bundle branch: There was slight fibrosis of the beginning of the left bundle branch. In addition, many fibers showed degenerative changes and early necrosis (Fig. 6). More apically there was marked fatty infiltration (Fig. 7). There were areas in which only a few Purkinje cells were seen in the midst of the fatty infiltration. Still more distally the degenerative and early necrotic changes in the fibers of the left bundle branch increased.

Fig. 7. Case 2. Section through lower part of left bundle branch, showing fibrosis and marked fatty infiltration. Weigert-van Gieson stain, ×24.

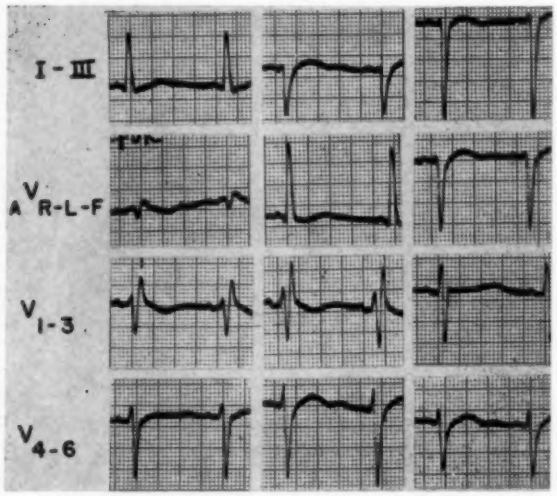

Fig. *8*. Electrocardiogram of Case 3. See text.

Blood supply to the conduction system: The ramus ostii cavae superioris showed no change, and the ramus septi fibrosi showed slight narrowing. There was marked narrowing of the arterioles of the septum but no change in the arteries.

CARDIAC PATHOLOGIC DIAGNOSES. (1) Arteriosclerotic heart disease, with cor pulmonale, with narrowing of the right main coronary artery and recent thrombus in the anterior descending coronary artery. (2) Old lateral wall infarct, with extension to the anterior and posterior walls and small scars in the septum. (3) Very recent acute infarct, involving the entire left ventricle, septum, and parts of the right ventricle, and parts of both atria. (4) Hypertrophy of the heart (right ventricle, moderate; left ventricle, slight). (5) Marked fibrosis of the right bundle branch, with slight fibrosis of the left bundle branch. (6) Very early recent infarction of both bundle branches.

Case 3. (A-52-56) R. G.

CLINICAL DATA. This 56-year-old white woman was admitted to Mount Sinai Hospital, on Feb. 3, 1956, because of intermittent epigastric pain which had been present for 3 weeks, and which had become severe on the night prior to admission. There was a 10-year history of severe rheumatoid arthritis, which had been treated with steroids for 4 years. Five years prior to admission, she underwent a cholecystectomy for cholelithiasis. There was also a history of anemia requiring several blood transfusions, about 9 months before admission.

On admission, the patient was acutely ill, with pallor and grunting respirations. The temperature was 98.6°F. but rose rapidly to 102°F. in 4 hours. The blood pressure was 122/82 mm. Hg, pulse 74 per minute, and respiratory rate 20 per minute. There was rigidity in the epigastrium, with epigastric tenderness.

Within 24 hours after admission, edema and induration of the area under the cholecystectomy scar were noted. Incision and drainage of a large abscess in the right upper quadrant was performed on the second hospital day. After this procedure the temperature declined to a low-grade febrile level. Because of the clinical impression of adrenal exhaustion, the patient was given daily intramuscular injections of 40 units of ACTH, gel.

Nine days after admission the patient had a brisk hematemesis and lapsed into shock. Blood transfusions and levarterenol were given. The bleeding subsided over a 48-hour period, but on the eleventh hospital day the patient had emesis of bright red blood and passed a copious tarry stool. Emergency laparotomy was performed, and a large posterior duodenal ulcer was exposed. A limited gastric resection was accomplished. After surgery the patient developed a right saphenous thrombophlebitis and had a septic temperature. She expired on Feb. 23, 1956, on the twentieth hospital day.

On admission, the hemoglobin was 6.6 Gm. per cent, red blood count 2,970,000, white blood count 16,900, with 83 per cent neutrophils, 9 per cent bands, 3 per cent lymphocytes, 3 per cent meta-

Fig. *9*. Case 3. Section through second portion of right bundle branch, showing fibrosis and fatty infiltration. Weigert–van Gieson stain, ×150.

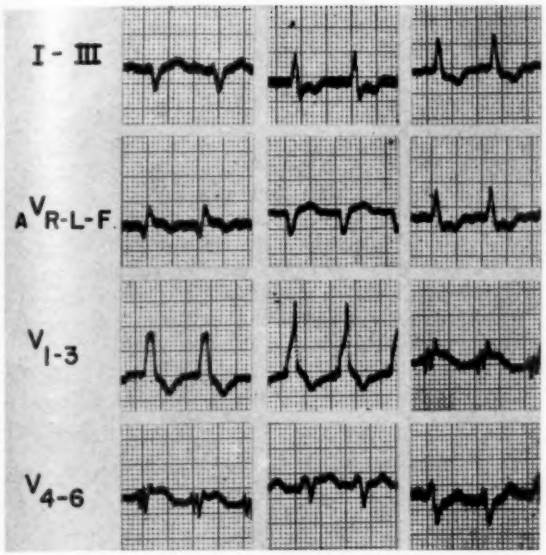

Fig. *10.* Electrocardiogram of Case 4. See text.

myelocytes, and 2 per cent myelocytes. Urinalysis showed a trace of albumin, numerous white blood cells, and 2-4 red blood cells per high-power field. On February 8, the serum sodium was 147.5 mEq. per liter, potassium 3.28 mEq. per liter, nonprotein nitrogen 3.7 mg. per cent, total protein 5.6 Gm. per cent, albumin 3.5 Gm. per cent, and globulin 2.1 Gm. per cent.

ELECTROCARDIOGRAPHIC FINDINGS. The electrocardiogram obtained on the fourth hospital day (Fig. 8), 2 weeks before death, showed a sinus rhythm, with a rate of 68 and P-R of 0.12 second. There was a marked left axis deviation in the frontal plane and a shift of the precordial transition zone to the left, suggesting left ventricular hypertrophy. On the other hand, the contour of the right-sided precordial leads, in association with slurring and prolongation of QRS (to 0.12 second) suggested the presence of a right-sided intraventricular, possibly bundle branch, block. The ST-T configuration in limb and precordial leads was abnormal and, although not characteristic, was considered consistent with left ventricular strain.

POSTMORTEM EXAMINATION. Aside from the findings in the heart, the pathologic diagnoses were: (1) bleeding gastric ulcer, with operative procedures; (2) dehiscence of gastrojejunostomy and duodenal stump; (3) acute hepatitis and splenitis; (4) acute adrenalitis; (5) acute and chronic pyelonephritis; (6) nephrosis; (7) pulmonary emphysema and fibrosis; (8) calculus in common bile duct at ampulla of Vater, with marked dilatation of the common and hepatic bile ducts.

Heart: gross examination: The heart weighed 380 grams. The epicardium was grayish red, dull, and granular. The endocardium of the right atrium was yellow. The mitral and tricuspid valves showed small gray verrucous projections on the atrial aspect, near the free margin. There was slight left and right ventricular hypertrophy. The myocardium of the right atrium showed an extensive zone of necrosis, extending from the entrance of the inferior vena cava to the entrance of the superior vena cava, and involving part of the sinoatrial nodal region. There was practically no atherosclerosis or narrowing of the large coronary arteries.

Heart: microscopic examination: *General pathologic change:* There was acute and subacute endocarditis of the mitral valve, with associated myocarditis with abscesses and small infarcts, and small organizing thrombi in the small arteries. This involved the anterior and posterior walls of the left and right ventricles, the ventricular septum, the left atrium, and, to a lesser extent, the atrial septum. *Right atrium:* There was a recent and organizing infarct of the right atrial appendage, with organizing fat necrosis and an organizing thrombus in one of the atrial arterial branches, and associated organizing pericarditis.

Conduction system: *S-A node:* The S-A node was infiltrated by lymphoid cells. *Approaches to the S-A node:* There was a complete recent infarct, involving all approaches to the S-A node, with the exception of the superior approaches. *Approaches to the A-V node:* A recent infarct was present in the inferior approaches to the node. *A-V node:* There were occasional macrophages in the node. *A-V bundle, penetrating:* This was the seat of mild and acute degenerative changes. *A-V bundle, branching:* This presented mild acute degenerative changes. Occasional mononuclear cells surrounded the bundle. There was moderate fibrosis of the right side of the bifurcation.

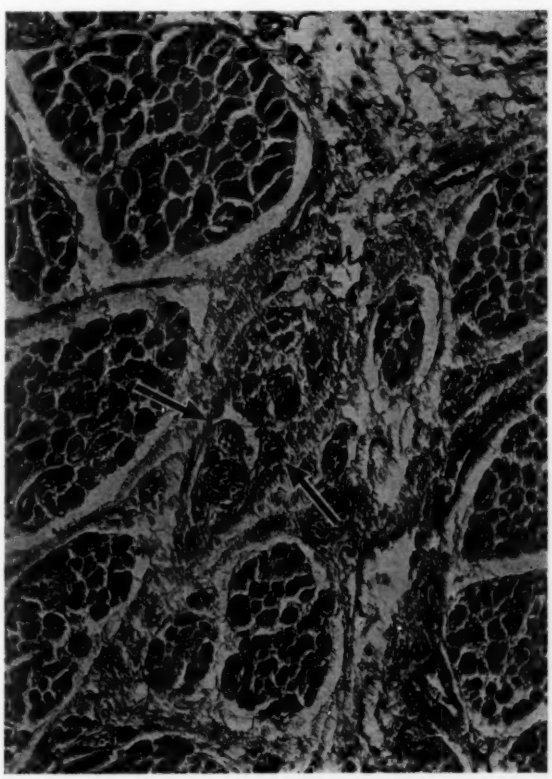

Fig. *11.* Case 4. Section through second portion of right bundle branch, showing marked fibrosis and elastosis. Weigert–van Gieson stain, ×150.

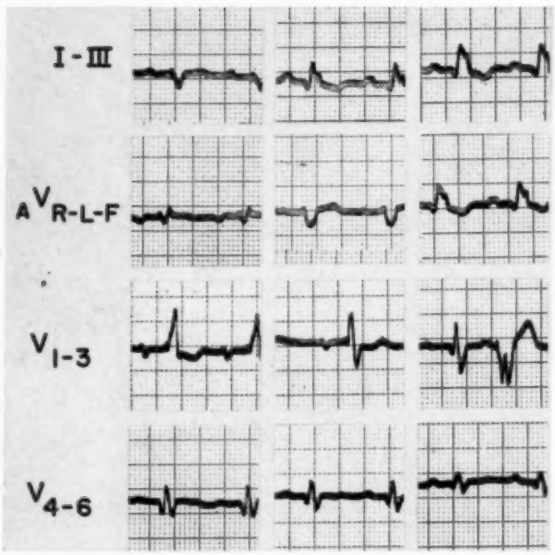

Fig. *12*. Electrocardiogram of Case 5. See text.

Right bundle branch: In the first portion there was moderate fibrosis, about one fifth of the structure being replaced. This was accompanied by focal acute degenerative changes and a scattering of mononuclear and lymphoid cells. In the second portion there was a progressive increase in the acute degeneration and early necrosis as it proceeded distally. The amount of fibrosis increased to about one-fourth replacement of the structure (Fig. 9), then decreased more distally. In the midst of the second portion, considerable fatty infiltration appeared (Fig. 9). The right bundle branch became divided into several parts, lying in fatty tissue with marked increase in acute degenerative change. In the third portion the right bundle branch showed marked fatty infiltration and a slight infiltration of lymphoid cells.

Left bundle branch: The beginning of the left bundle branch showed considerable acute degenerative and early necrotic change, more intense than in the beginning of the right bundle branch, with a slight infiltration of mononuclear cells. This became more intense distally, with considerable focal necrosis, and fatty infiltration.

Blood supply to the conduction system: The ramus ostii cavae superioris and the ramus septi fibrosi showed no change. The arteries and arterioles of the septum showed acute vascular degeneration.

CARDIAC PATHOLOGIC DIAGNOSES. (1) Acute and subacute endocarditis of the mitral valve, with associated myocarditis with abscesses and small infarcts. (2) Organizing thrombus in a right atrial artery, with organizing infarct of the right atrium. (3) Acute vascular degeneration. (4) Acute fibrinous pericarditis. (5) Fibrosis of the right bundle branch, moderate. (6) Acute degenerative and early necrotic changes of both bundle branches, moderate. (7) Acute and organizing infarction of the approaches to the sinoatrial and atrioventricular nodes.

Case 4. (A-125-55) H.R.

CLINICAL DATA. This 65-year-old white man with a long-standing history of angina pectoris and atrial fibrillation was admitted to the Mount Sinai Hospital on June 24, 1955, with severe pain and numbness of the left leg of 8 hours' duration. There was no history of previous claudication. On admission, the patient was acutely ill, with cyanosis and profuse diaphoresis. The apical rate was 140, and the respirations were 50 per minute. The heart was not enlarged. An abdominal aortic pulse was palpated faintly, but all pulses distal to this area were absent. There was a bluish discoloration and mottling of both lower extremities, extending to the lower abdominal wall on the right. Despite vasopressor amines and intravenous dextran the patient expired in shock 1½ hours after admission.

On admission, the hemoglobin was 13.73 Gm. per cent, the red blood count was 4.45 million, and the white blood count was 5,600, with a normal differential.

ELECTROCARDIOGRAPHIC FINDINGS. The electrocardiogram (Fig. 10) revealed a rapid and regular ventricular action at a rate of 136, caused by an ectopic atrial tachycardia, possibly atrial flutter with a 2:1 ventricular response. There was a pattern of a right bundle branch block (QRS of 0.12 second) in association with right ventricular hypertrophy. ST-T deviations in the precordial leads suggested recent injury effects in the anteroseptal region, but there was no evidence of myocardial necrosis due to a confluent infarct.

POSTMORTEM EXAMINATION. Aside from the findings in the heart, the pathologic diagnoses were: (1) chronic passive hyperemia, fibrosis and edema of the lungs; (2) bilateral hydrothorax; (3) chronic passive hyperemia and peripheral fibrosis of the liver; (4) severe atherosclerosis of the aorta and

Fig. *13*. Case 5. Section through distal part of second portion of right bundle branch, showing almost complete replacement by fibrous and elastic tissue. Weigert–van Gieson stain, ×80.

iliac arteries; (5) recent and organizing thrombi of the abdominal aorta and iliac arteries; (6) subacute splenitis.

Heart: gross examination: The heart weighed 500 grams. The left ventricle was markedly hypertrophied, and the right was moderately hypertrophied. There was severe atherosclerosis, with almost complete occlusion of the left circumflex and anterior descending coronary arteries and marked narrowing of the ostium of the right coronary artery. In addition, the left anterior descending coronary artery presented a recent thrombus, 3 to 4 cm. from its ostium, which completely occluded the lumen. An infarct of uncertain age was noted in the posterior septum, and in the subendocardial portion of the anterior and posterior walls, petering out toward the lateral wall.

Heart: microscopic examination: *General pathologic change:* There was generalized arteriosclerosis and necrosis. *Left ventricle:* There was an old subendocardial infarct with foci of organizing infarct spread throughout both the anterior and posterior walls, with a superimposed very early recent subendocardial infarct. *Right ventricle:* There was an old and organizing infarct involving the anterior and posterior walls, more marked in the posterior than in the anterior walls, and less marked than in the left ventricle. *Ventricular septum:* There was an old and organizing, mostly subendocardial, infarct on the left ventricular side, which extended through the wall in some areas in both the anterior and the posterior parts. In addition, there was a very recent infarct, more severe in the posterior than in the anterior septum. *Right atrium:* There were old and organizing zones of infarction. *Left atrium:* There was an old subendocardial infarct with foci of acute degeneration. *Atrial septum:* Fibrosis with focal fat necrosis was present.

Conduction system: *S-A node:* There were no changes. *Approaches to the S-A node:* There was marked fibrosis with small scars, involving the superior and medial connections and, to a lesser extent, the inferior connections. There was organizing fat necrosis around the S-A node. *Approaches to the A-V node:* There were no changes. *A-V node:* There were scattered mononuclear cells at the beginning of the node. At the end there was minimal fibrosis. *A-V bundle, penetrating:* There was fibrosis at the distal portion, with some irregularity in staining of the fibers, with mononuclear cells on the periphery. *A-V bundle, branching:* There was considerable fibrosis in the bundle, with foci of early necrosis, and frank necrosis at spots of junction of the fasciculi of the left bundle branch.

Right bundle branch: The beginnings of the first portion presented increased elastosis, followed by small areas of fibrosis. In this region there were acute degenerative changes but no frank necrosis. In the second portion the fibrosis and elastosis increased markedly (Fig. 11), with a reduction of 50 per cent of its parenchyma; this became less more distally. In the third portion, severe acute degenerative changes but no necrosis persisted to the end.

Left bundle branch: There were acute degenerative changes and early necrosis of many fasciculi at the junction with the bundle throughout the entire posterior radiation. Degenerative and early necrotic changes in the Purkinje fibers were present throughout the bundle branch, including the periphery.

CARDIAC PATHOLOGIC DIAGNOSES. (1) Arteriosclerotic and arteriolosclerotic heart disease, with marked narrowing of the left circumflex and anterior descending coronary arteries and narrowing of the ostium of the right coronary artery. (2) Recent thrombus in the anterior descending coronary artery. (3) Old subendocardial infarct of the septal, anterior, and posterior walls of the left ventricle and extension into the anterior and posterior walls of the right ventricle. (4) Focal organizing infarct of these walls. (5) Very recent subendocardial infarct of the anterior, septal, and posterior walls of the left ventricle. (6) Marked hypertrophy of the left ventricle and moderate hypertrophy of the right. (7) Moderate fibrosis of the atrioventricular bundle. (8) Moderate fibrosis and elastosis of the right bundle branch, with moderate acute degenerative changes. (9) Marked acute degeneration and early necrosis, focal, of the left bundle branch.

Case 5. (A-109-55) M.K.

CLINICAL DATA. This 62-year-old white man was admitted to Mount Sinai Hospital on May 3, 1955, in congestive failure. He had had pneumonia 6 weeks previously, for which he had been admitted to another hospital. After his discharge he had noted progressive swelling of the legs and swelling of the abdomen, with moderate shortness of breath.

On examination, the blood pressure was 108/60 mm. Hg, and the pulse was 88 and regular. The heart was enlarged to the left, with bilateral râles and pleural effusion. There was massive ascites and marked edema of the lower extremities. The patient showed some improvement on digitalis and diuretics, but suddenly and unexpectedly died in shock on June 9, 1955. The nonprotein nitrogen on admission was 60, and the urinalysis showed 1-plus albumin.

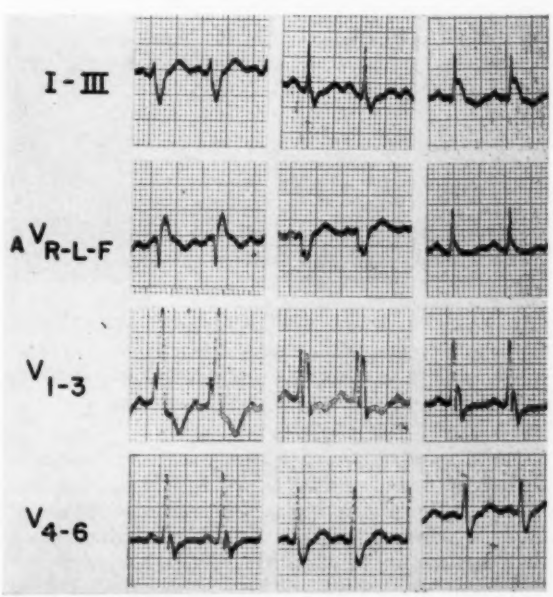

Fig. *14.* Electrocardiogram of Case 6. See text.

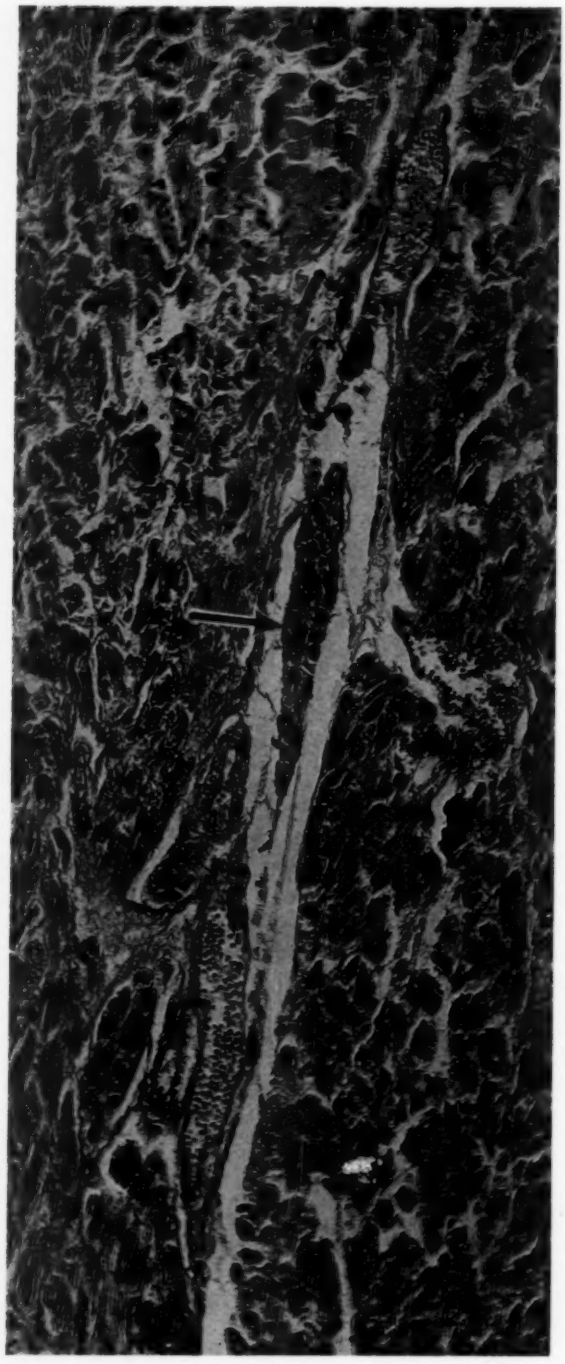

Fig. *15A*. Case 6. Section through second portion of right bundle branch, showing very small localized lesion. Partial replacement. Weigert–van Gieson stain, ×150.

ELECTROCARDIOGRAPHIC FINDINGS. An electrocardiogram taken on May 7, 1955, showed complete right bundle branch block. The electrocardiogram (Fig. 12) taken on June 6, 1955, showed sinus rhythm (rate of 95 and P-R of 0.18 second), with occasional premature ectopic beats, probably of ventricular origin. The ventricular complexes of the dominant beats revealed a pattern of right bundle branch block (QRS of 0.14 second) in association with right ventricular hypertrophy. Prominent Q waves in Leads II, III, aV_F, and V_3 to V_6 suggested the presence of anterolateral and posterior wall infarction of undetermined age.

POSTMORTEM EXAMINATION. Aside from the findings in the heart, the pathologic diagnoses were: (1) chronic passive hyperemia of the lungs; (2) pulmonary fibrosis and edema; (3) bilateral hydrothorax; (4) chronic pleuritis of the right lung, with marked fibrous adhesions; (5) ascites; and (6) pitting edema of the lower extremities.

Heart: gross examination: The heart weighed 650 grams. The right and left ventricles were both markedly hypertrophied, the left more than the right. The anterior descending coronary artery presented severe atherosclerosis and was completely occluded by an old calcified plaque 7 cm. from its origin. The left circumflex artery was also occluded 4 cm. from its ostium by a calcified mass. The right main coronary artery presented a recent, organizing thrombus about 4 cm. from the ostium. Large areas of the anterior wall of the left ventricle appeared to be scarified. Areas of what was interpreted as more recent organizing infarctions were noted in the lateral and posterior walls. At the base of the posterior wall there was a brownish-yellow area, which extended into the septal and anterior walls.

Heart: microscopic examination: *General pathologic change:* Arteriolonecrosis was present throughout. *Left ventricle:* There was an old subendocardial infarct involving the anterior and posterior walls, with extension through the wall in the basal portion of the posterior wall, and with spots of organization subepicardially in the anterior wall. *Right ventricle:* Focal spots of organizing infarct were noted in both walls. *Ventricular septum:* The old and organizing infarct involved both the anterior and posterior septa, with a recent infarct on the left side of the posterior septum. *Atria and atrial septum:* The right atrium showed a small organizing infarct of the appendage, with generalized fibrosis. The left atrium showed no change. The atrial septum showed fibrosis.

Conduction system: *S-A node:* There were occasional dispersions of lymphoid cells. *Approaches to the S-A node:* There were foci of organizing and old infarct. *Approaches to the A-V node:* There were foci of organizing infarct with focal fibrosis. *A-V node:* There was an occasional infiltration of mononuclear cells. *A-V bundle, penetrating:* There was some irregularity in staining of cytoplasm of cells. An occasional vessel showed necrosis. *A-V bundle, branching:* There was slight fibrosis.

Right bundle branch: In the beginning of the first portion there was slight to moderate fibrosis which replaced about one fourth of the substance of the bundle branch. This increased to one third near the end. In addition, there were slight acute degenerative changes. In the beginning of the second portion the fibrosis increased and replaced about one half of the substance of the bundle branch. Progressively downward there was almost complete replacement of the bundle branch (Fig. 13). This was a widespread lesion, and was accompanied by necrosis of the few remaining cells. Near the end of the second portion, fatty infiltration appeared

and the fibrosis diminished greatly, although the necrosis persisted. The third portion of the right bundle branch showed moderate fatty infiltration, with foci of infiltration of lymphoid cells, and very minimal fibrosis.

Left bundle branch: The beginning of the left bundle branch showed considerable necrotic changes with an infiltration of neutrophils and lymphoid cells, with slight fibrosis. More distally, these changes persisted, as the bundle lay in the acute infarct. Focally, there appeared to be fatty infiltration, with dissolution of fibers and an infiltration of mononuclear cells. The peripheral Purkinje cells showed severe degenerative changes.

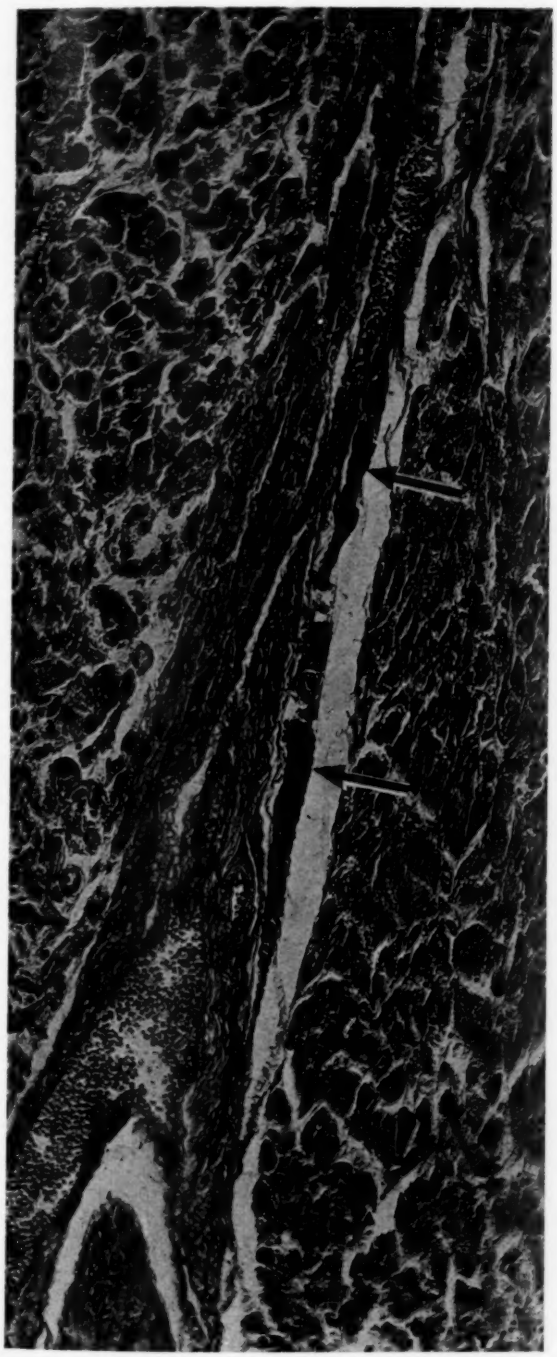

Fig. *15B*. Case 6. Section through second portion of right bundle branch, showing very small localized lesion. Complete replacement. Weigert–van Gieson stain, ×150.

CARDIAC PATHOLOGIC DIAGNOSES. (1) Arteriosclerotic heart disease, with old occlusion of the right coronary artery and the left circumflex coronary arteries. (2) Old and organizing infarct of the anterior wall, septum, and posterior and lateral walls of the left ventricle. (3) Organizing infarct of the anterior and posterior walls of the right ventricle. (4) Recent infarct of the septum. (5) Marked left and moderate right ventricular hypertrophy. (6) Marked fibrosis of the right bundle branch and minimal fibrosis of the left bundle branch. (7) Organizing and old infarct at the approaches to the sinoatrial and atrioventricular nodes. (8) Slight fibrosis of the branching portion of the atrioventricular bundle.

Case 6. (A-41-55) H.M.

CLINICAL DATA. This 66-year-old white man, a controlled diabetic, was admitted to the Mount Sinai Hospital on Feb. 17, 1955, because of crampy, lower abdominal pain which had been present for several hours. On admission, the temperature was 99.8°F., the pulse was 96 per minute, the respiratory rate was 22 per minute, and the blood pressure was 138/70 mm. Hg. There was a large reducible right inguinal hernia, and tenderness in the right lower quadrant, but without rigidity or spasm. On the second hospital day, after several episodes of vomiting and a loose stool, a flat-plate of the abdomen suggested obstruction of the small bowel. At this time, gastric suction was instituted. On February 19, the patient was subjected to an exploratory laparotomy under low spinal anesthesia, with release of an incarcerated loop of ileum from an internal hernial sac. Thirty minutes after induction of anesthesia the blood pressure fell from 120/70 to 90/50 mm. Hg, but with levarterenol it returned to normal levels and the operative procedure was completed. The postoperative course was complicated by acute gastric dilatation, relieved by intubation. On the second postoperative day, a hypokalemic alkalosis was treated with replacement therapy. On the fourth postoperative day the patient became disoriented, lethargic, and febrile. He died later that day (Feb. 24, 1955) shortly after a fever of 106°F. was reached. On admission the hemoglobin was 14.3 Gm. per cent, red blood count was 4.63 million, and white blood count was 13,500, with a shift to the left. On the third postoperative day, the white blood count was 11,200, with a shift to the left.

ELECTROCARDIOGRAPHIC FINDINGS. The ECG (Fig. 14) of Feb. 23, 1955, revealed a sinus tachycardia of 136, with P-R of 0.14 sec. and premature ectopic beats, most likely ventricular in origin. There were characteristic features of a right bundle branch block, with QRS prolongation to 0.14 sec., as well as of right ventricular hypertrophy.

POSTMORTEM EXAMINATION. Aside from the findings in the heart, the pathologic diagnoses were: (1) pulmonary edema with bronchopneumonia; (2) pulmonary emphysema; and (3) fibrosis and fatty infiltration of the pancreas.

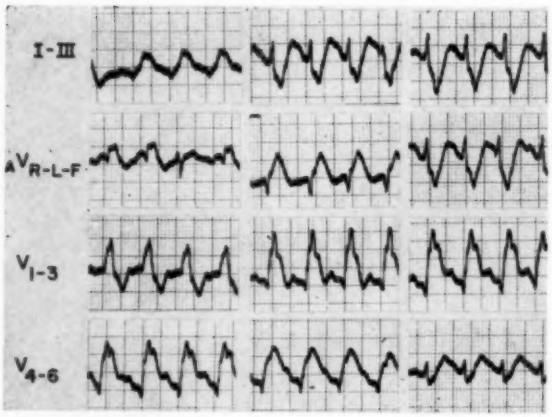

Fig. *16.* Electrocardiogram of Case 7. See text.

Heart: gross examination: The heart weighed 440 grams. There were moderate hypertrophy and dilatation of the right atrium and ventricle and slight hypertrophy of the left atrium and ventricle. The right coronary artery, 3 cm. from its origin, was completely occluded by atheromatous plaques and what appeared to be a recent thrombus. The left coronary artery showed atherosclerosis but no narrowing. There was a yellowish mottling of the endocardial surface of the left side of the septum and anterior and posterior walls of the left ventricle.

Heart: microscopic examination: *General pathologic change:* There was generalized acute vascular degeneration. The point of obstruction in the right coronary artery showed a recent and organizing thrombus. *Left ventricle:* There was minimal fibrosis of the anterior wall, and slight fibrosis of the posterior wall. *Ventricular septum:* There was slight fibrosis with small scars in the anterior and posterior septa. *Right ventricle:* There was moderate fibrosis with small scars in the anterior and posterior walls. *Atria and atrial septum:* There was slight fibrosis and elastosis of the right atrium and septum, and slight fibrosis of the left atrium.

Conduction system: *S-A node:* There was no change. *Approaches to the S-A node:* Slight fibrosis was noted. There was a small scar directly adjacent to the S-A node. *Approaches to the A-V node:* There was slight fibrosis in the upper and lower approaches. There was an occasional focus of macrophages immediately adjacent to the node. *A-V node:* There was minimal fibrosis. *A-V bundle, penetrating:* There was minimal fibrosis. *A-V bundle, branching:* There was a slight infiltration of macrophages.

Right bundle branch: The beginning of the right bundle branch showed an infiltration of macrophages. In the second portion the structure first showed slight fibrosis (Fig. 15*A*), and then rapidly it became completely fibrotic (Fig. 15*B*). The completely fibrotic lesion measured only 0.2 mm. After this lesion the right bundle branch became normal again. More peripherally in the second portion there were occasional macrophages around the structure, with fatty infiltration. In the third portion, slight acute degenerative changes appeared, with an infiltration of lymphoid cells and mononuclear cells.

Left bundle branch: There was a focal infiltration of macrophages. More peripherally there was considerably fatty infiltration.

Blood supply to the conduction system: The ramus ostii cavae superioris, the ramus septi fibrosi, and the arteries and arterioles of the septum showed no narrowing.

CARDIAC PATHOLOGIC DIAGNOSES: (1) Arteriosclerotic heart disease, with recent and organizing thrombus with obstruction of the right main coronary artery. (2) Moderate fibrosis of the septum and anterior and posterior walls of the right ventricle and slight fibrosis of the anterior and posterior walls of the left ventricle. (3) Acute vascular degeneration. (4) Hypertrophy of the heart (right ventricle, moderate; left ventricle, minimal). (5) Slight fibrosis of the approaches to the sinoatrial node and minimal fibrosis of the atrioventricular node and bundle. (6) Marked fibrosis of the right bundle branch. (7) Slight acute degenerative changes of both bundle branches. (8) Fatty infiltration of both bundle branches.

Case 7. (A-175-55) S.L.

CLINICAL DATA. This 62-year-old white woman was admitted to Mount Sinai Hospital on Oct. 2, 1955, with a history of retrosternal pressure associated with diaphoresis of 3 days' duration, increasing in severity on the day of admission.

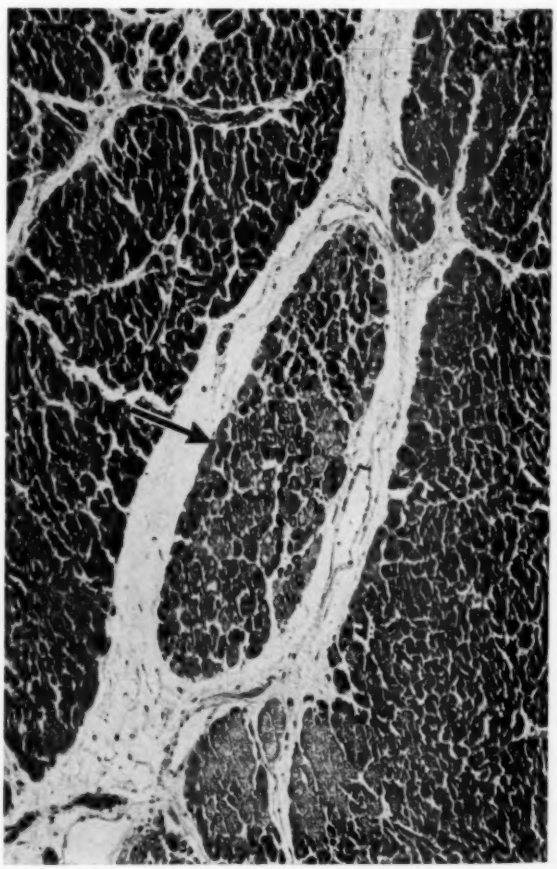

Fig. *17.* Case 7. Section through the right bundle branch, showing early necrosis, surrounded by recent infarct of the myocardium. Hematoxylin-eosin stain, ×95.

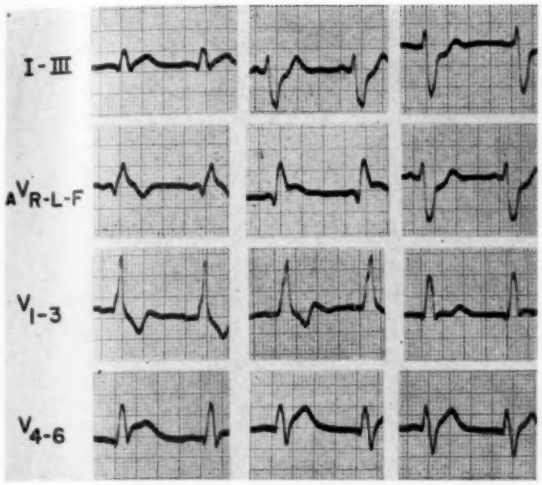

Fig. *18*. Electrocardiogram of Case 8. See text.

Past history revealed no indication of heart disease. A carcinoma had been detected on radical mastectomy 2½ years previously, and the patient was receiving testosterone for bony metastasis to the pelvis. On admission she was in shock, cyanotic, had coarse râles in both lung fields, and the neck veins were distended. She expired 1½ hours after admission.

ELECTROCARDIOGRAPHIC FINDINGS. The electrocardiogram (Fig. 16) showed a sinus tachycardia (rate of 136 and P-R of 0.18 second) with premature ectopic beats, probably of ventricular origin, frequently occurring in pairs. The ventricular complexes had a bizarre appearance, with characteristic features of both a right bundle branch block (QRS of 0.14 second) and recent anterior and lateral wall infarction. The predominance of R waves in the right precordial leads was ascribed to right ventricular hypertrophy.

POSTMORTEM EXAMINATION. Aside from the findings in the heart, the pathologic diagnoses were: (1) radical mastectomy for carcinoma of the breast; (2) metastasis to the third lumbar vertebra; (3) hirsutism; (4) pulmonary fibrosis and arteriolosclerosis; and (5) adenoma of the thyroid.

Hear gross examination: The heart weighed 290 grams. There was questionable hypertrophy of both ventricles. There was marked thickening and narrowing of the beginning of the anterior descending artery. At one point a red thrombus completed the occlusion. The other arteries showed no narrowing. The myocardium of the left ventricle in the most superior portion of the anterior wall presented a distinct area of softening, and there were slight hemorrhagically discolored zones in the anterior wall adjacent to the septum.

Heart: microscopic examination: *General pathologic change:* There was generalized acute arteriolitis and periarteriolitis. Focal small zones of metastasis with organizing myocarditis involving the left ventricle anteriorly and posteriorly and the septum were noted. *Left ventricle:* In addition to the above-mentioned features, there was irregularity in staining of fibers in the anterior wall, less in the posterior wall. *Right ventricle:* There was some irregularity in staining in the anterior wall at the base and in the inferior wall. *Ventricular septum:* In addition to the general changes described above, there was fibrosis of the right side of the septum at the base posteriorly and generalized fibrosis anteriorly. There was also irregularity in staining of the fibers, more marked anteriorly. *Atria and atrial septum:* There were no remarkable changes.

Conduction system: *S-A node:* There were no changes. *Approaches to the S-A node:* There was an occasional small zone of organizing infarction. *Approaches to the A-V node:* There was no appreciable change. *A-V node:* There was some lymphoid cell infiltration, with slight fibroblastic proliferation. *A-V bundle, penetrating:* There was no appreciable change. *A-V bundle, branching:* In the beginning there was slight fibrosis of the right side of the bundle, which became moderate at the bifurcation.

Right bundle branch: The first portion showed slight fibrosis. The second portion lay in an area of acute degenerative changes of the myocardium, and the right bundle branch itself showed severe acute degenerative changes (Fig. 17). This persisted to the moderator band.

Left bundle branch: In the beginning there was slight fibrosis. Throughout its course, it showed slight acute degenerative changes.

Blood supply to the conduction system: In the ramus ostii cavae superioris there was no narrowing; in the ramus septi fibrosi there was moderate narrowing. In the arteries and arterioles of septum there was marked arteriolosclerosis with narrowing.

CARDIAC PATHOLOGIC DIAGNOSES. (1) Arteriosclerotic heart disease, with recent thrombus in the anterior descending coronary artery. (2) Very recent anteroseptal ischemic changes. (3) Focal small metastases of carcinoma of the breast to the myocardium, with focal organizing myocarditis. (4)

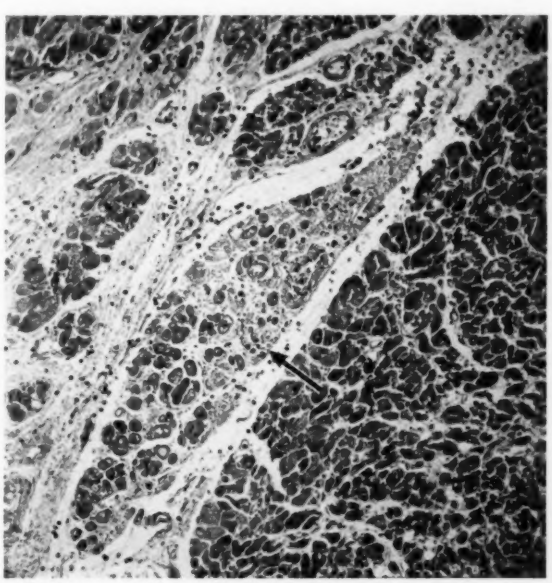

Fig. *19*. Case 8. Section through second portion of right bundle branch, showing fibrosis, necrosis and an infiltration of neutrophils. Hematoxylin-eosin stain, ×115.

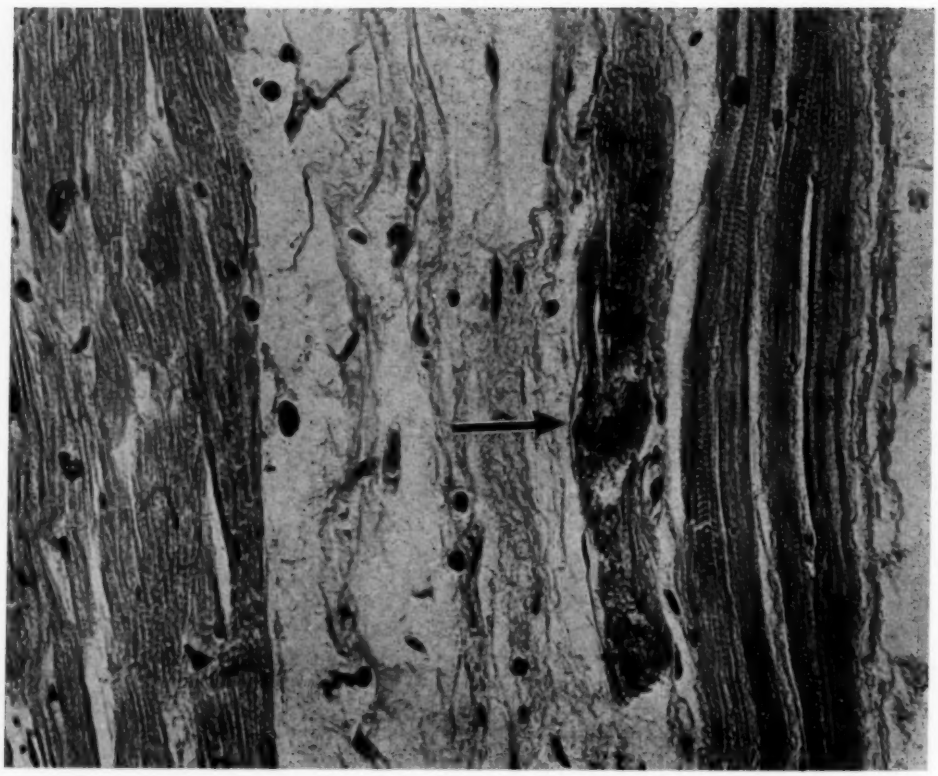

Fig. *20*. Case 8. Section through Purkinje fibers of left bundle branch, showing necrosis. Hematoxylin-eosin stain, ×340.

Acute arteriolitis and periarteriolitis. (5) Slight fibrosis of the right side of the atrioventricular bundle, branching. (6) Severe acute degenerative changes of the right bundle branch, and slight acute degenerative changes of the left bundle branch.

Case 8. (A-95-55) M.O.

CLINICAL DATA. This 67-year-old white man was admitted to Mount Sinai Hospital on May 14, 1955, with a history of gradually increasing pain in both elbows of 3 days' duration, followed by a sudden onset of severe prostrating substernal distress associated with diaphoresis and dyspnea. There was no previous history of precordial distress. He was critically ill on admission and in peripheral vascular collapse. Despite the use of lanatoside-C and levarterenol to combat shock and failure, the patient failed to respond, expiring 8 hours after admission. The white blood count was 20,550, with 78 per cent neutrophils, 6 per cent bands, 13 per cent lymphocytes, 2 per cent monocytes and 1 per cent myelocytes. The red blood count was 6,350,000, with a hemoglobin of 17.6 Gm. per cent.

ELECTROCARDIOGRAPHIC FINDINGS. The electrocardiogram (Fig. 18) showed a sinus rhythm at a rate of 73, with a P-R of 0.14 second. The QRS was prolonged to 0.16 second, with features of right bundle branch block and right ventricular hypertrophy in the precordial leads. However, a marked left axis deviation with small QRS complexes in Leads I and aV_L also suggested left ventricular hypertrophy with anterolateral wall infarction. S-T deviations in precordial leads indicated that the infarct, at least in its lateral part, was of recent date.

POSTMORTEM EXAMINATION. Aside from the findings in the heart, the pathologic diagnoses were: (1) pulmonary edema, bilateral, with early bronchopneumonia; and (2) fatty metamorphosis of the liver.

Heart: gross examination: The heart weighed 540 grams. Both the left and right ventricles were markedly hypertrophied. The subendocardial half of the entire anterior wall of the left ventricle, the left aspect of the entire ventricular septum, and the adjacent portion of the posterior wall were diffusely hemorrhagically discolored. A small area of hemorrhage, measuring 1.0 cm. in greatest dimension, was noted in the myocardium of the anterior wall of the right ventricle. The right coronary artery was the dominant artery and presented moderate sclerotic changes but no narrowing. The left anterior descending artery showed severe sclerotic changes and was occluded by a fresh thrombus 2.0 cm. from the ostium. The left circumflex artery was likewise occluded by an organizing thrombus near its ostium.

Heart: microscopic examination: *General pathologic change:* There was diffuse acute arteriolar degeneration and acute pericarditis. The acute infarct present in the various walls was typified by marked hemorrhage and an infiltration of neutrophils. *Left ventricle:* Most of the anterior wall and parts of the posterior wall were involved in the acute infarct. *Right ventricle:* The anterior wall showed foci of acute infarct. In addition, there was an occasional scar and zone of fibrosis. The posterior wall showed only a small zone of recent infarct There were occasional zones of fibrosis with smal

scars. Both walls showed marked fatty infiltration. *Ventricular septum:* The entire septum was involved in the acute infarct. In addition, small zones of organizing infarct were noted subendocardially in the posterior portion. There were also small scars on the right side of the septum proximally and throughout the septum distally, with considerable fibrosis.

Conduction system: *S-A node:* There was no change. *Approaches to the S-A node:* The posterior crest showed slight fibrosis. *A-V node and its approaches:* There were no changes. *A-V bundle, penetrating and branching:* There were no changes.

Right bundle branch: The first portion showed little change. The second portion showed considerable fibrosis, with necrosis, and an infiltration of neutrophils (Fig. 19). The recent infarct persisted in the third portion.

Left bundle branch: As the left bundle branch proceeded distally, there was increasing acute degeneration, going on to frank necrosis (Fig. 20) with an infiltration of neutrophils.

CARDIAC PATHOLOGIC DIAGNOSES. (1) Coronary sclerosis, with severe narrowing of the anterior descending artery. (2) Recent thrombus, with occlusion of the anterior descending artery, and organizing thrombus of the left circumflex artery. (3) Focal fibrosis with small scars of the posterior septum and right ventricle. (4) Massive recent hemorrhagic infarct involving the entire ventricular septum, anterior wall, and the apex maximally, the posterior wall moderately, and the anterior and posterior walls of the right ventricle slightly. (5) Recent infarction of both bundle branches. (6) Moderate fibrosis of the right bundle branch. (7) Marked hypertrophy of both ventricles.

Case 9. (A-182-55) G.S.

CLINICAL DATA. This 70-year-old white man, known to have been hypertensive for 20 years, was admitted to the hospital on Jan. 22, 1955, because of protracted chest pain. For 2 years prior to admission the patient had shown signs and symptoms of congestive heart failure, which was relieved by digitalization, periodic mercurial diuretics, and bed rest. Angina, which had existed for 1 year, usually occurred after meals, and was relieved by nitroglycerin. On the night of admission the patient was awakened by protracted precordial distress, and he entered the hospital in collapse. On examination he complained of severe chest pain, was in severe distress, cold and clammy. The blood pressure was 110/70 mm. Hg; the ventricular rate was 140 and grossly irregular. The heart was enlarged to the left, and a systolic murmur was heard at the apex maximally. Bibasilar râles were present. On the day of admission the patient lapsed into more severe shock, requiring levarterenol for 2 days to maintain his blood pressure. Progressive improvement occurred, and he was discharged on March 13, 1955, approximately 7 weeks after admission. After discharge, he experienced angina on slight emotional or physical provocation and suffered recurrent congestive failure. Three days prior to his last admission his substernal pain increased in frequency and intensity and was unrelieved by nitroglycerin. At this time, he was given Demerol, oxygen, and mercurial diuretics, with some relief. He was readmitted to the hospital on Oct. 10, 1955, with severe dyspnea and protracted chest pain. On admission he was pulseless, in profound shock, semistuporous, cyanotic, with Cheyne-Stokes respirations. He failed to respond to vasopressor therapy and expired 5 hours after admission.

ELECTROCARDIOGRAPHIC FINDINGS. The electrocardiograms (Fig. 21) during the patient's first admission, taken on Jan. 22, 1955, showed, at first, atrial fibrillation, with a rapid ventricular response (averaging 130 per minute), and, later, on Feb. 8, 1955, sinus rhythm at a rate of 80, with P-R of 0.14 second. There were signs of left ventricular hypertrophy and of an incomplete left bundle branch

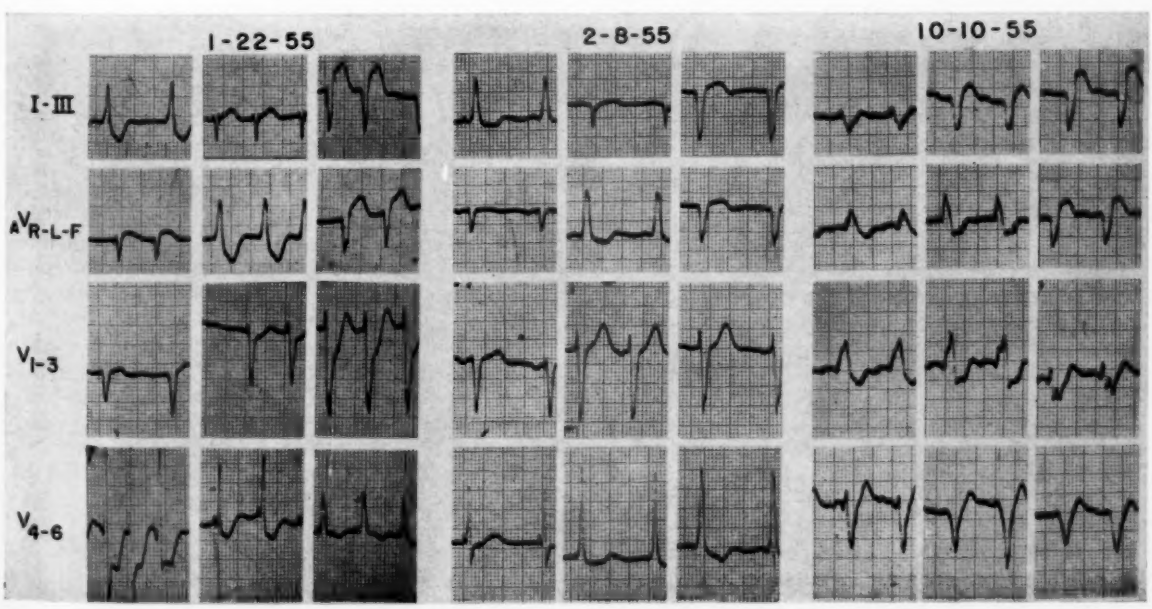

Fig. 21. Electrocardiograms of Case 9. See text.

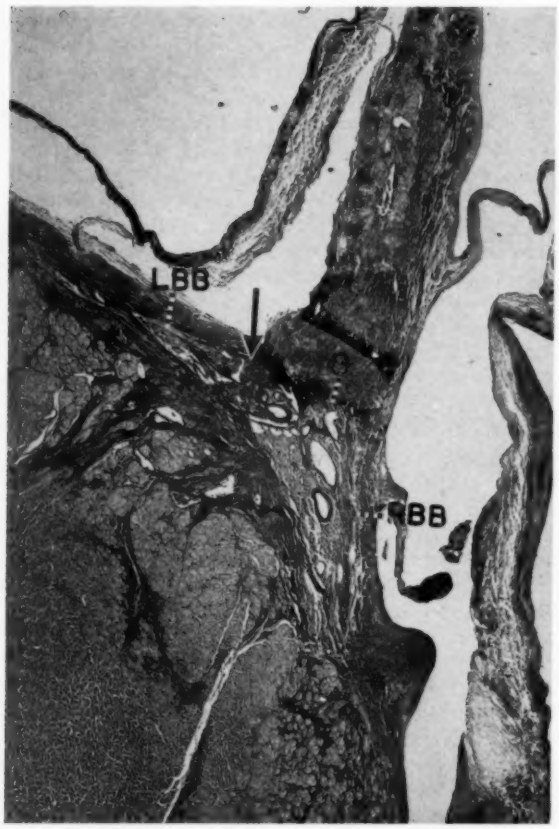

Fig. *22*. Case 9. Section through bifurcation into right bundle branch and anterior radiation of left bundle branch, showing old scar. Weigert–van Gieson stain, ×25.

block (QRS of 0.12 second). On January 22, these appeared to be modified by fresh injury of the posterior wall, but changed later, on February 8, to alterations consistent with posterior wall infarction.

In the last record, taken on Oct. 10, 1955, during the final admission, there was a sinus tachycardia of 110, with a slightly prolonged P-R interval (0.22 second). The contour of the ventricular beats had changed to that of a right bundle branch block (QRS of 0.16 second) associated with right ventricular hypertrophy, and appeared to be modified by digitalis and/or recent posterior wall injury. Left ventricular hypertrophy and the left-sided intraventricular block were no longer evident.

POSTMORTEM EXAMINATION. Aside from the findings in the heart, the pathologic diagnoses were: (1) arteriolar nephrosclerosis, with acute vascular degeneration and early necrosis; (2) generalized arteriolar sclerosis and acute vascular degeneration and early necrosis; (3) marked pulmonary emphysema, with fibrosis and pulmonary arteriolosclerosis; (4) chronic passive hyperemia of the liver, with central necrosis and periportal fibrosis; (5) chronic passive hyperemia of the spleen, with fibrosis; (6) bronchopneumonia; (7) chronic pancreatitis; and (8) chronic adrenalitis and periadrenalitis.

Heart: gross examination: The heart weighed 500 grams. There was a diffuse fibrinous exudate over the heart. There was marked hypertrophy of both ventricles, and a relatively greater hypertrophy of the right ventricle. An old infarct with aneurysmal dilatation was noted in the basilar half of the posterior wall and the most basilar part of the posterior septum. In addition, a recent infarct was present, involving the entire septum, extending through to the right ventricle, and extending over the apical third of the posterior septum, and the apical two thirds of the anterior septum, in which region it also involved the lateral wall. It also extended to the apical two fifths of the anterior and the inferior walls of the right ventricle. There was a small mural thrombus in the left ventricle. There was marked sclerosis of the coronary arteries, with narrowing of the anterior descending and the right main artery, with a recent thrombus at the beginning of the anterior descending branch.

Heart: microscopic examination: *General pathologic change:* There was marked arterioslcerosis and arteriolosclerosis of the coronary arteries. *Left ventricle:* There was an old infarct involving most of the subendocardial regions of the left ventricle. In some areas in the posterior wall this extended intramurally, and occasionally subepicardially. In addition, there was a recent infarct in both the anterior and posterior walls. *Right ventricle:* The recent infarct extended into the anterior and posterior walls. In addition, there were foci of organizing and old infarction in the anterior and posterior walls. *Ventricular septum:* Most of the septum was involved in the recent infarct. In addition, the left ventricular subendocardial portion showed an old infarct. *Atria and atrial septum:* Many regions of the right atrium showed areas of recent and organizing infarcts, whereas the left atrium and septum showed a recent infarct.

Conduction system: *S-A node:* There was acute degeneration and early necrosis. *Approaches to the S-A node:* The posterior crest showed many zones of recent, organizing, and old infarction. Likewise, Wenckebach's bundle and the myocardium at the inferior approaches to the node showed many areas of recent infarction. There were some acute degenerative changes of the myocardial fibers at the approaches to the A-V node, but no frank infarction. *A-V node:* There were no changes. *A-V bundle, penetrating:* There were no changes. *A-V bundle, branching:* There were acute degenerative changes at its junction with the left bundle branch fasciculi. Also an organizing infarct, involving part of the cross section of the bundle, was present. In other spots there was fibrosis. A scar was noted at the left side of the bifurcation (Fig. 22), which, however, did not interrupt the bundle.

Right bundle branch: In the first portion there was moderate fibrosis with acute degeneration of its fibers. In the second portion there was early necrosis. In the third portion there again was early necrosis (Fig. 23), as it lay in a recent infarct.

Left bundle branch: The beginning of the left bundle branch showed acute degenerative changes. Slightly more distally, it was the seat of early necrosis, as it lay in the midst of an acute infarct. Throughout the remainder of its course there was focal fatty infiltration. Here and there, Purkinje fibers showed necrosis and zones of fibrosis.

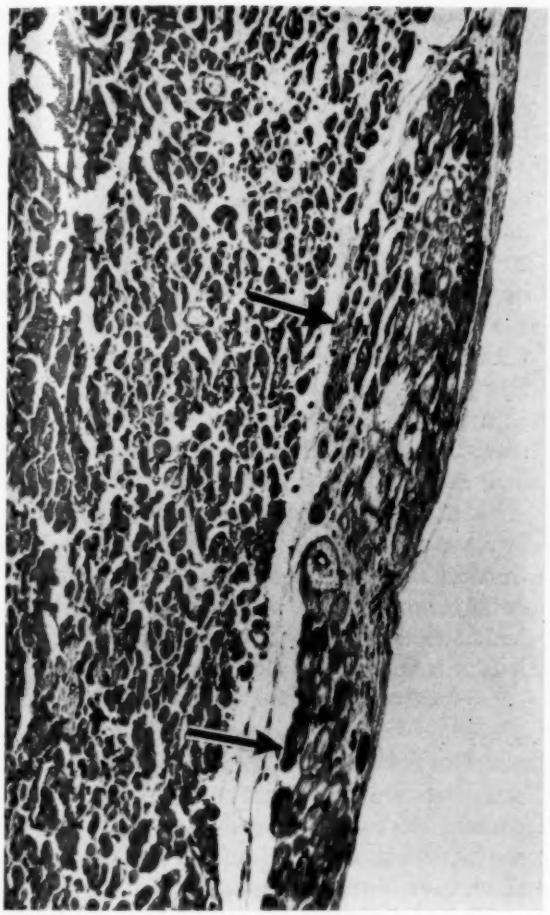

Fig. *23.* Case 9. Section through third portion of right bundle branch. Hematoxylin-eosin stain, ×68.

Blood supply to the conduction system: The ramus ostii cavae superioris showed no changes. The ramus septi fibrosi showed marked sclerosis with narrowing. The arterioles of the septum showed narrowing.

CARDIAC PATHOLOGIC DIAGNOSES. (1) Marked coronary sclerosis, with severe narrowing of the right coronary artery in the region of the ramus ostii cavae superioris, left anterior descending artery, and ramus septi fibrosi. (2) Recent thrombus in the anterior descending artery. (3) Massive old subendocardial infarct, involving the posterior walls of both ventricles, the left ventricular side of the septum, with less involvement of both anterior walls. (4) Massive recent infarct, involving both anterior walls, most of the septum, with less involvement of both posterior walls. (5) Organizing and old scar of the branching portion of the bundle of His, with acute degenerative changes. (6) Focal necrosis of the sinoatrial node. (7) Acute degeneration and early necrosis of both bundle branches.

Discussion

In an attempt to correlate anatomic lesions of the bundle branches with bundle branch block patterns of the electrocardiogram it must be emphasized that the term "complete bundle branch block" used in routine electrocardiography does not of necessity imply a complete anatomic disruption of the continuity of one of the bundle branches. Conceivably, a unilateral delay of impulse conduction through a functionally altered portion of a bundle branch could produce in the electrocardiogram the pattern of a complete bundle branch block if this retardation exceeds the time necessary for spread of impulses from the contralateral ventricle through the ventricular septum. The latter time has been estimated to be between 0.04 and 0.06 second.[11-13] Hence, the term "complete bundle branch block" has to be understood in a functional rather than a strictly anatomic sense.

With this reservation in mind, we can divide, for the purpose of correlation, the 9 cases of our series into three groups: (1) cases in which the electrocardiographic findings of complete right bundle branch block (RBBB) must be correlated with old lesions in the right bundle branch (Cases 1,3,5,6); (2) cases in which the correlation must be made with recent and old lesions (Cases 2,4,8,9); and (3) cases in which the correlation must be made with recent lesions (Case 7).

In Group 1, there is electrocardiographic evidence that complete RBBB was present 1 year (Case 1), 1 month (Case 5), and 2½ weeks (Case 3) before death. In all of these, old lesions in the right bundle branch were found. In Case 6, the electrocardiogram showing complete RBBB was taken within 24 hours of death. Since no recent lesion is present in the right bundle branch in this case, the correlation is again made with the old lesion present. Here, then, we have excellent correlation between the electrocardiographic complex and an old lesion in the right bundle branch. In Group 2, the electrocardiogram showing complete RBBB was taken within 24 hours of death, and the length of time the RBBB might have been present is unknown. Hence, all lesions present in the right bundle branch must be correlated with this complex. In all 4 cases (Cases 2,4,8,9), significant lesions in the right bundle branch were found. If the RBBB was of recent vintage, then the correlation is excellent. If it was long-stand-

ing, then 3 of the 4 cases show significant old lesions, and Case 4 shows a questionably significant old lesion. Hence, the correlation is good. In Group 3 (Case 7), there was one case in which the electrocardiogram was taken within 24 hours of death, and only recent lesions in the right bundle branch were found. Here again the correlation is good, as in the previous group. Thus, in our entire series there is excellent correlation with old lesions of the right bundle branch, and good correlation with combined or recent lesions.

However, in this evaluation of the electrocardiographic findings, we began with no basic assumptions, except that the complex RBBB is related to some pathologic change in the heart. Table II presents the various pathologic changes found in the 9 hearts examined. As concerns lesions in the left bundle branch, it can be seen that in Group 1 there are no significant old lesions in this structure. There is thus no correlation with the electrocardiographic complex of complete RBBB. Hence, the over-all correlation of lesions of the bundle branch with the electrocardiogram is excellent. In Group 2, significant recent lesions were found in Cases 2, 4, 8, and 9, which were as marked as the lesions in the right bundle branch. In these cases the old lesions were insignificant. In this group, therefore, correlation of complete RBBB with lesions of the left bundle branch is uncertain. In Group 3, Case 7 showed an insignificant recent lesion in the left bundle branch. If the data of our entire series are taken as a whole, there does not appear to be a correlation between the electrocardiographic pattern of complete RBBB and lesions of the left bundle branch. This is of some interest in view of the historical controversy as to what comprises the electrocardiographic complex of RBBB.

Table II also indicates the lack of correlation between the electrocardiographic abnormality of complete RBBB and right or left ventricular hypertrophy, lesions in other parts of the conduction system, and lesions in the myocardium of the right ventricular wall. Although considerable lesions were found in the left ventricular wall and the septum in 7 of 9 cases, in 2 cases the changes were insignificant, casting doubt upon the immediate importance of this actor in the production of the electrocardiographic abnormality of complete right bundle branch block. Therefore, an objective analysis of our findings would seem to indicate a significant correlation only with lesions of the right bundle branch.

It must be pointed out, however, that our method of sampling is relatively poor as concerns the peripheral Purkinje network on both sides, and, hence, these are not properly evaluated in our analysis. Likewise, no quantitative analysis of dilatation of chambers was made in this series. Furthermore, it is self-evident that the significance of the connection between lesions of the right bundle branch and the electrocardiographic pattern of complete RBBB is contingent upon control studies. Erickson and Lev,[14] in their study of the normal heart in all age groups, did not find such lesions. However, no studies have yet been made to see whether there are pathologic hearts exhibiting these lesions without the electrocardiographic complex of complete RBBB. It is also self-evident that our work concerns itself only with arteriosclerotic heart disease, and our findings cannot necessarily be transferred to rheumatic heart disease, congenital heart disease, and cor pulmonale.

The pathologic change in the right bundle branch was most often widespread. However, in Case 3 it was a minute lesion. In most cases the lesions were incomplete, indicating the breech between the morphologic findings and the physiologic concept of complete RBBB discussed above. The second part of the right bundle branch was mostly involved, but sometimes the first and third parts were also involved. In no case was the first or third parts involved alone in this series. As concerns the old pathologic change, this usually consisted of a partial fibrotic replacement of the muscle cells. In two cases this was almost complete. Several cases showed a proliferation of elastic tissue in the replacement. As concerns the recent pathologic change, this consisted of either frank necrosis of muscle cells or acute degenerative change—that is, irregularity in staining of the cytoplasm with the nucleus still intact. The former was sometimes associated with infiltration of neutrophils and lymphoid cells.

The foregoing morphologic study of complete right bundle branch block corrobo-

rates in general the monumental work of Lenègre.[1] There is a slight point of variance. In our series, as in the work of Mahaim[15] and Yater,[16] both bundle branches were involved in complete right bundle branch block whenever correlation was made with recent lesions.

Electrocardiographically, the presence of a right bundle branch block was reflected in the right precordial leads in 6 cases by a more or less slurred R wave, and in 3 by an rR′ or qR complexes (Table II). This does not conform with the usual frequency of these patterns, the latter two being ordinarily the more common ones. Two anatomic features predominating in the material studied may be responsible for this, namely, recent and old extensive infarction of the left ventricle or right ventricular hypertrophy. The absence of myocardial infarction in Case 3, the only one with an rSR′ pattern, could indeed suggest a dependence of the QRS configuration over the right precordium on the condition of the myocardium of the left ventricle. However, in Case 5, with another common pattern (rR′), massive left ventricular infarction was present. Kossmann and associates[17] have pointed out that it is virtually impossible to visualize a situation in which, in the presence of arteriosclerotic heart disease, so much destruction could occur that, from the standpoint of muscle mass alone, the right ventricle would predominate over the left. Therefore, it appears more likely that the presence, to a varying degree, of right ventricular hypertrophy in all of the cases was the factor which determined the QRS configuration of the right precordial leads in the material presented.

In contrast to the accuracy in the diagnosis of right ventricular hypertrophy, 5 cases with anatomically left ventricular hypertrophy could not be recognized as such electrocardiographically, and 1 case (Case 7) in which such a diagnosis was made showed only a slight degree at autopsy. Furthermore, in Case 9 an incomplete left bundle branch block associated with left ventricular hypertrophy (demonstrated at autopsy) completely disappeared after the development of a right-sided ventricular conduction defect. It would appear, therefore, that in arteriosclerotic heart disease the combination of a "complete" right bundle branch block with right ventricular hypertrophy can entirely obscure electrocardiographic manifestations of left ventricular hypertrophy, with or without an incomplete left bundle branch block.

Summary

1. The conduction system and the entire heart in 9 cases in which the electrocardiographic pattern was that of complete right bundle branch block were studied histopathologically. Eight of these cases were instances of coronary heart disease, and one of myocarditis.

2. There was positive correlation between the electrocardiographic pattern of complete right bundle branch block and the presence of significant pathologic changes in the right bundle branch.

3. There was no correlation with any other pathologic finding in the heart.

4. Thus, the electrocardiographic pattern of complete right bundle branch block has an anatomic base in significant lesions in the right bundle branch in coronary heart disease. The anatomic base of this complex in congenital or other types of heart disease is not discussed in this work.

5. Right ventricular hypertrophy was correctly diagnosed electrocardiographically in the presence of complete right bundle branch block. In coronary heart disease the combination of complete right bundle branch block and right ventricular hypertrophy may obscure the electrocardiographic manifestations of left ventricular hypertrophy, with or without an incomplete left bundle branch block.

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Comparative proximity and remoteness characteristics of conventional electrocardiographic leads

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The Einthoven limb leads have historically been treated as remote leads, and the unipolar precordial leads as proximity leads. On the other hand, the direct relationship of the unipolar extremity leads to the Einthoven leads was initially emphasized[1]; later, in accordance with Wilson's electroposition concept, proximity characteristics were ascribed to these leads.[2]

The introduction of the lead field into experimental electrocardiography has facilitated a more accurate expression of heart-lead relationships.[3,4] By definition, the lead field is the electrical field which is produced in the body when one unit of direct electrical current is caused to flow from the positive to the negative terminal of an electrocardiographic connection. Because of Helmholtz principle of reciprocity the gradient at any point within the field is identical to the lead vector at that point.[3]

In order to assess the relative remoteness or proximateness of various electrocardiographic connections, we mapped lead-field isopotentials upon the body surface of 7 human subjects and in the sagittal plane of a homogeneous torso model.

Methods and materials

In the portion of this study which was devoted to human subjects, we mapped the body surface traces of the bipolar lead-field isopotentials by means of a previously described technique.[5] In the analysis of Einthoven connections, each of the lead pathways was reciprocally energized with 1-milliampere square wave impulses of direct current. In the case of the augmented unipolar extremity leads the technique was modified in such a way that each of two bipolar lead connections was simultaneously energized with 0.5-milliampere square wave impulses of direct current. The specific connections and directions of reciprocal energization which we employed are as follows: Lead aV_R energization = −0.5 Ma. through Lead I pathway and −0.5 Ma. through Lead II pathway; Lead aV_L energization = 0.5 Ma. through Lead I pathway and −0.5 Ma. through Lead III pathway; Lead aV_F energization = 0.5 Ma. through Lead II and Lead III pathways, each.

The electrocardiographic model employed in this study was constructed from

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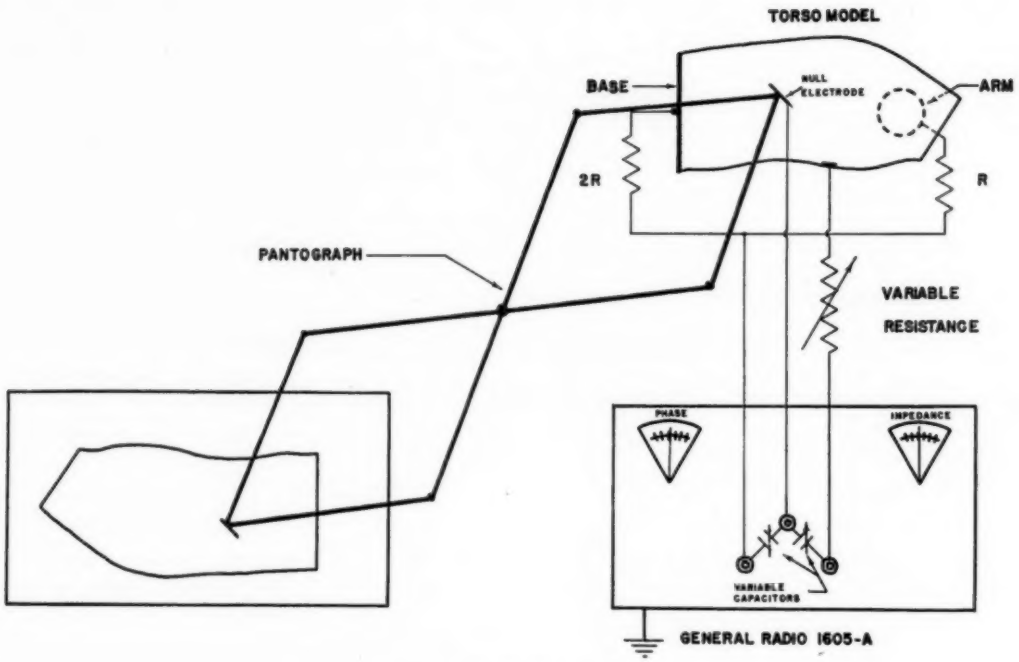

Fig. *1.* Schematic representation of lead-field mapping technique in torso model. The torso model (*upper right*) is in the left lateral recumbent position and filled with a suitable electrolyte. The lead connection illustrated consists of a midline "precordial exploring" electrode paired to the Wilson central terminal. The latter is formed from the base and left arm electrodes which have unequal resistors according to the principle of electrical images. The null or mapping electrode is located at an arbitrary site in the sagittal plane of the model. This site represents a null point when the lead connection has been balanced and a null reading obtained by the impedance comparator (*lower right*). The mapping electrode is then moved along a null (equipotential) line, while the map is simultaneously transcribed from the model by a 1:1 pantograph (*lower left*). Further discussion in text.

a left-half plaster-of-Paris mold of a human torso, including the left arm. After the cast was waterproofed with several coats of an epoxy resin, the distal arm end and distal trunk portion were occluded with sealed-in aluminum plates, and the neck end terminated in a fitted Lucite plate. With the model maintained in the left lateral recumbent position it was filled with ordinary tap water with a specific resistivity of 6,255 ohm-centimeters. It, thus, formed an open-faced electrolytic tank in which the surface of the fluid corresponded to the sagittal plane of the original subject. An electrode was located at any desired point about the boundary of the sagittal plane by applying silver conducting paint* to a semicircular area, 1 cm. in diameter, just beneath the surface of the electrolyte. The aluminum plates were coated with the same material to minimize voltaic effect.

*Walsco Silver Print No. 36, Walsco Electronics Manufacturing Co., Rockford, Ill.

The open construction of the model offers the particular advantage of making the interior, particularly the sagittal plane, readily accessible to an electrode probe. Thus it is a relatively simple matter to use a 1:1 pantograph, as shown schematically in Fig. 1, as an aid in the plotting of lead-field isopotentials. The mapping procedure was further simplified by the use of a commercially available impedance comparator (see Appendix).

A total of 10 lead connections was studied. The 6 conventional extremity connections (Einthoven and augmented unipolar) were studied in 7 human subjects. Maps of all 6 limb connections were plotted in 4 cases; Einthoven leads only—in 1 case; augmented unipolar leads only—in 2 cases. The following 4 lead fields were mapped upon the sagittal plane of the model: midsternal-V (near V_2), midvertebral-V (near VB), midsternal-F (near CF_2), neck–lower extremities ("Y"). In a human subject the latter lead connection corresponds to

Table I. *Proximity and remoteness characteristics of conventional ECG leads*

Lead	*Grade*	*Subjects*
I	Intermediate*	5
II	Semiremote	5
III	Remote	5
aV_R	Semiremote	6
aV_L	Semiproximate	6
aV_F	Remote	6
"V_2"	Proximate	Model
"VB"	Proximate	Model
"CF_2"	Semiproximate*	Model
"Y"	Remote	Model

*Significant curvilinear distortion.

equally weighted resistors on the lower extremities and an equally weighted resistor on each side of the neck.

Lead characteristics were determined by a comparison of the general form of the experimental lead fields (as extrapolated to the cardiac region) to ideal proximate and remote lead fields (Fig. 2). On the basis of this qualitative visual comparison the various lead connections were graded as remote, semiremote, intermediate, semiproximate, and proximate. Significant curvilinear distortion was also estimated.

Results

In the human subject phase of the study no remarkable individual differences in the form of the fields could be detected. The subjects were normal young adults with body builds ranging from asthenic to sthenic.

The 10 leads which were studied are classified as to their relative proximity or remoteness in Table I. Four representative lead fields are illustrated in Figs. 3, 4, 5, and 6. These 4 fields demonstrate a progressive transformation from proximate to remote in the order of presentation. Both the flow lines and isopotential lines are illustrated in the torso model fields (Figs. 3 and 6), whereas only the isopotential lines are illustrated in the human subject fields (Figs. 4 and 5).

The first field (Fig. 3) is that of a unipolar precordial lead and has been graded as proximate. This field was plotted in the torso model and approximates Lead V_2—since the lead connection was formed by pairing a midsternal exploring electrode at the level of the fourth intercostal space with the Wilson central terminal. Although the field corresponds to the ideal proximate lead, there is a slight symmetrical, curvilinear flaring of the flow lines. Such flaring, however, should actually tend to exaggerate the proximity effect.

The second field (Fig. 4) is that of Lead aV_L as mapped upon a human subject, and has been graded as semiproximate. This lead is illustrated because it is more proximate than the other 5 conventional extremity leads, but less than the degree evident in the unipolar precordial lead. This decrease in proximity effect is not entirely a consequence of greater anatomic distance, since it is also a result of the fact that the left shoulder represents an area electrode rather than a point electrode.

The third field (Fig. 5) is that of Lead aV_F as mapped upon a human subject, and has been graded as remote. It can be seen that the equipotential lines are relatively uniform in the cardiac region as in the case of the ideal remote lead, and that curvilinear distortion is minimal. Leads aV_F and III appear to be the most remote of the 6 conventional extremity leads.

The fourth field (Fig. 6) is that of a synthetic lead formed by connecting the neck with both lower extremities. In a human subject this connection would correspond to equally weighted resistors on the lower extremities and an equally weighted re-

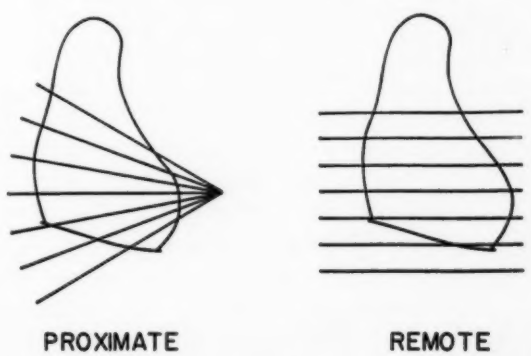

Fig. 2. Ideal lead fields. Lead field flow lines in the case of an infinite homogeneous conducting medium when the electrode is near the heart (*proximate*), and when the electrode is withdrawn to a great distance (*remote*). The flow lines are superimposed upon the cardiac silhouette. Further discussion in text.

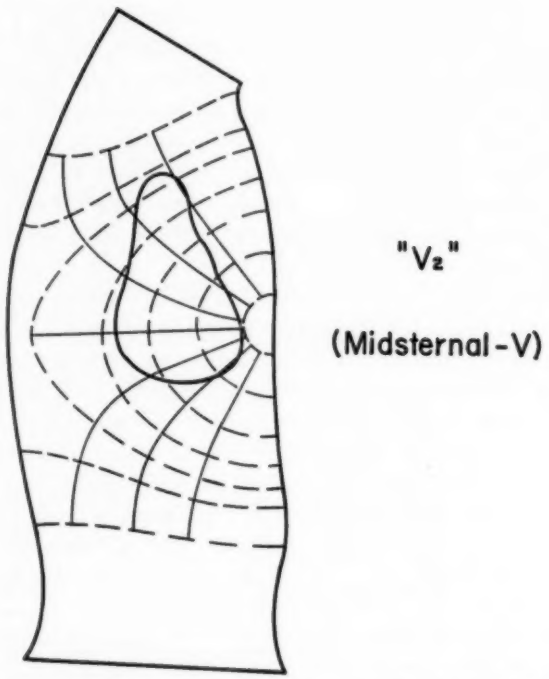

Fig. *3*. Lead field of a unipolar precordial lead which has been graded as proximate. Both the flow lines (*solid*) and isopotential lines (*dashed*) are illustrated, and the cardiac silhouette has been superimposed. This field was plotted in the model.

sistor on each side of the neck. This field was mapped in the model and has been graded as remote. Although similar to Lead aV_F, there is even less curvilinear distortion. Because of its orientation and uniformity this lead represents an ideal "Y" or vertical remote lead.

Discussion

The experimental lead fields were graded as to their degree of approximation to ideal proximate and remote lead fields. Such lead fields, as shown in Fig. 2, are in essence those that would occur in an infinite homogeneous conducting medium if the exploring electrode were located relatively near to the heart (in the case of the proximate lead), and if it were withdrawn to a large distance (in the case of the remote lead). In both cases the flow lines are rectilinear, but, as one might expect from their hypothetical origin, they appear to emanate from a point in the proximate lead and they are parallel in the remote lead. The situation is analogous to a chest roentgenogram with the film in contact with the patient's chest; if the tube is brought near to the chest, the tissues nearer the tube are exaggerated, whereas if the tube is withdrawn to a large distance, this proximity effect is not evident.

The proximate lead fulfills the requirements of the solid angle concept, whereas the remote lead may be analyzed according to the well-known lead vector principle. In terms of an equivalent multipolar cardiac generator it may be further stated that the remote lead responds only to the dipolar components, whereas the proximate lead detects not only the dipolar but also the higher-order axially oriented components.

Although the flow lines are rectilinear in the case of the ideal leads, a certain element of curvilinear distortion occurred in all the conventional electrocardiographic leads. In certain instances, particularly the anterior and posterior unipolar chest leads, there was a symmetrical flaring of the flow lines through the cardiac region—at least in the sagittal plane. Although this feature prevents strict conformity to the solid angle concept, it nevertheless tends to augment the proximity effect. In other instances, particularly in Leads I and CF_2, there was an asymmetric flaring or "pinching together" of the flow lines within the cardiac region. When of significant degree such distortion militates against strict approximation to the two ideal fields. Although some distortion is

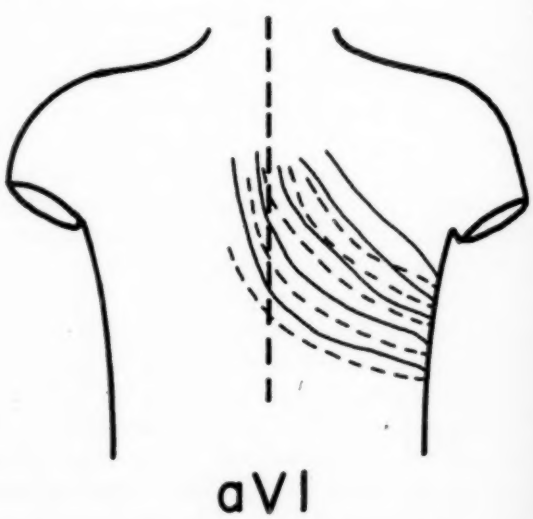

Fig. *4*. Typical Lead aV_L field map of a normal human subject which has been graded as semiproximate. Only the isopotential lines are illustrated, both anteriorly (*solid lines*) and posteriorly (*dashed lines*). Interval between isopotential lines is 2.0 mv.

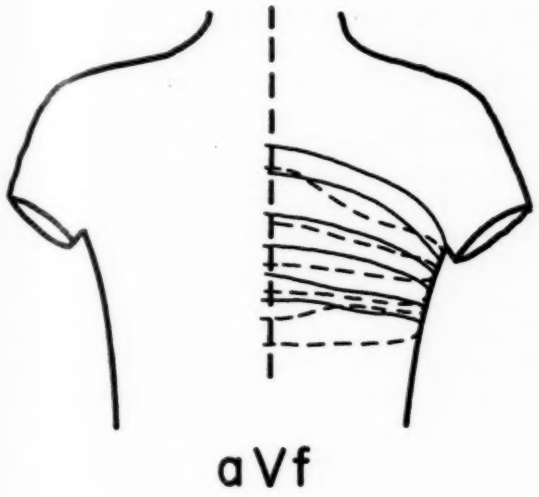

Fig. 5. Typical Lead aV_F field map which has been graded as remote. Same subject as in Fig. 4. Only the isopotential lines are illustrated, as in Fig. 4. Interval between isopotential lines is 1.5 mv.

present in the conventional leads, it is to be emphasized that both types of ideal leads may also be designed in the case of the human subject—at least in principle.

There are certain features of the representative fields (Figs. 3-6) and the classification (Table I) which have theoretical significance, and thus appear worthy of further emphasis:

I. As already noted, some curvilinear distortion is inherent in all the conventional electrocardiographic leads, and thus they are not ideal in a strict sense. However, with two exceptions, such distortion is slight and, therefore, the majority tend to approach the ideal.

II. Although, in general, the 6 extremity leads are relatively remote in comparison to the 2 unipolar chest leads, some of them nevertheless exhibit considerable deviation from the ideal remote lead. Thus, whereas 4 of the connections were graded as remote or semiremote, Lead I was graded as intermediate and Lead aV_L as semiproximate.

A. Leads aV_R and aV_F are relatively remote, which is incompatible with the requirements of the electroposition concept.

B. Leads aV_F and III best approach the ideal remote lead. However, the synthetic neck–lower extremity connection appears superior to aV_F as a remote "Y" lead.

C. The left shoulder connection introduces greater proximateness, manifest especially in Leads aV_L and I. This feature undoubtedly contributes to the configuration and variation of the Burger triangle. This represents a confirmation of Frank's studies in which the importance of the left arm attachment in the production of dipole-location errors was emphasized.[6]

III. Both unipolar chest leads ("V_2", "VB") studied are proximate, and this effect is actually somewhat exaggerated because of symmetrical, curvilinear flaring.

IV. Significant asymmetrical curvilinear distortion was noted in Leads I and CF_2. Therefore, these leads possess more complicated characteristics—with neither solid angle nor lead vector analysis being strictly applicable.

Although certainly informative, the studies which form the basis of this report are admittedly crude. The results are descriptive rather than quantitative. In the studies performed upon human subjects it was necessary to perform the mapping upon the body surface with extrapolation to the interior cardiac region, whereas during the torso model phase the mapping was limited to a single plane.

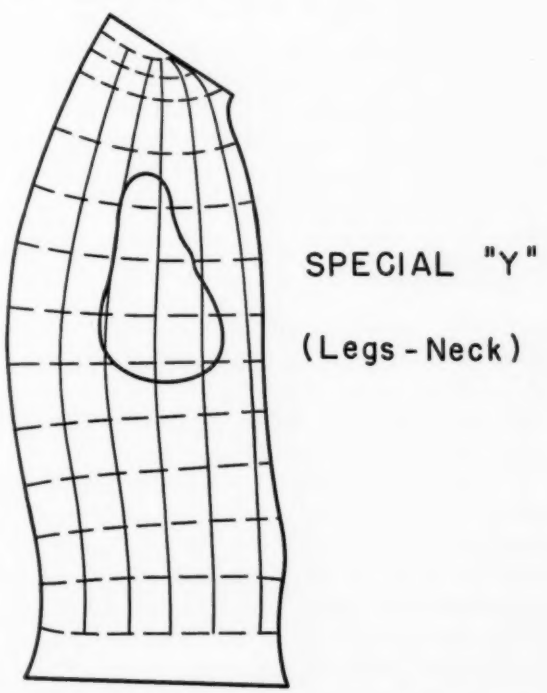

Fig. 6. Lead field of the neck–lower extremity connection which has been graded as remote. Both the flow lines (*solid*) and equipotential lines (*dashed*) are illustrated, and the cardiac silhouette has been superimposed. This field was plotted in the model.

However, with recent proposals concerning the application of equivalent multipoles to electrocardiographic analysis[7-9] and with the more recent introduction of the lead tensor concept,[10] it is possible to perform a more advanced type of experimental analysis. In essence, it appears quite likely that a technique can be developed which consists of constructing a homogeneous torso model patterned after a given subject, and then resolving numerous leads fields into their spherical harmonic components. It should then be possible to compute the derived equivalent multipolar components from the corresponding electrocardiograms recorded from the original human subject. The number of leads required to determine the equivalent cardiac generator through the nth order multipole is $n(n + 2)$. Therefore, in the event that an equivalent dipole + quadripole should be found adequate for representation of the human heart, it might be concluded that routine clinical electrocardiograms, which consist of 8 independent leads, contain all the diagnostic information that can be obtained from body surface electrocardiography. Preliminary results from a study of 8-lead cancellation, which is now in progress in this laboratory, indicate that multipolar representation through only the quadripole term may suffice for clinical purposes.

Hopefully, then, detailed lead-field analysis may help to answer a number of important and interesting questions in electrocardiography.

Summary

1. The proximity and remoteness characteristics of 10 conventional lead connections were estimated by a comparison of experimental lead fields with ideal proximate and remote lead fields.

2. The experimental lead fields were determined by mapping the isopotential function upon the body surface of 7 human subjects and in the sagittal plane of a homogeneous torso model. A simplified mapping technique in electrolytic models is introduced and described.

3. Certain theoretical implications of the various lead characteristics are discussed.

4. Some of the limitations of the present study are noted, and the possibility of performing a more advanced type of experimental analysis in the future is briefly considered.

Appendix

I. Impedance comparator technique. The procedure of lead-field mapping in electrolytic tank models is greatly simplified by the use of a commercially available impedance comparator* which gives a null reading when connected to two identical electrical impedances. The device operates at decade steps of frequency from 100 to 100,000 cycles per second, inclusive; at maximum sensitivity the impedance difference indicator covers a range of ± 0.3 per cent, and the phase angle difference indicator a range of ± 0.003 radians.† A frequency of 1,000 cycles per second was utilized in the present study.

The equipment employed in the torso model study is shown schematically in Fig. 1. The external resistances of the lead connections were sufficiently large to minimize alterations in the field due to possible variations in internal resistance. With the electrode probe at any arbitrary location immediately beneath the surface of the electrolyte, a null reading was obtained by balancing the external impedances. With this balance maintained the probe was then moved along the null pathway, and in this manner it traced an equipotential line. As illustrated in Fig. 1, a 1:1 pantograph served as an aid in the mapping process. The procedure proved to be quite rapid, with slightly less than 1 hour generally being required to map the isopotentials of a single lead connection.

II. Electrical images. The electrocardiographic model was a left-half model of a human torso, and the lead-field mapping was performed in the sagittal plane. According to the principle of electrical images, lead-field mapping is limited to configurations which are symmetrical with respect to the sagittal plane. For this reason any torso surface electrode which is not applied to the midline is electrically equivalent to two equally weighted electrodes—the actual one together with an electrical

*General Radio Impedance Comparator Type 1605-A, General Radio Company, Cambridge, Mass.

†A later model is specified to have three times these sensitivities.

image which is "mirrored" by the sagittal plane.

The Wilson central terminal in the model consisted of the base and left arm electrodes united to a common terminal. Although the base electrode is not identical to a left leg electrode, it can nevertheless be considered a very good approximation. Because of the principle of electrical images the left arm electrode was provided with twice the weight of the base electrode. Thus, the Wilson central terminal was equivalent to 3 equally weighted electrodes: the base, the left arm, and the mirror image of the left arm (i.e., the right arm).

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Effects of intravenous lanatoside-C upon cardiodynamics in patients with mitral stenosis and regular sinus rhythm

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Previous studies have shown that the most consistent effects of digitalis preparations are increases in stroke volume and cardiac output, but only in subjects with myocardial failure.[1-9] Changes in pressure in the lesser circulation and cardiac chambers vary according to the type of heart failure existing when the drug is administered. In patients with left ventricular failure, digitalis produces decreases in pulmonary arterial pressures but no change in right ventricular end-diastolic pressure. In patients with right ventricular failure, digitalis usually causes a reduction in right ventricular end-diastolic pressure. When pulmonary hypertension due to a restricted pulmonary vascular bed is the cause of right heart failure, the increased cardiac output is frequently accompanied by an increase in pulmonary arterial systolic pressure. Davis, Howell, and Hyatt[7] have demonstrated in dogs that when right heart failure is produced by constriction of the pulmonary artery, the increase in cardiac output and decrease in diastolic pressures of the right heart after acute administration of digoxin are associated with a rise in right ventricular systolic pressure. In combined ventricular failure, pulmonary arterial pressures may show variable changes, depending upon several factors, notably the initial pulmonary arterial pressures, the level to which stroke output increases, and the relative degrees of improvement in right and left ventricular functions.

It would be of interest to extend such studies to include the effects of digitalis preparations in patients who have obstruction to the passage of blood from the lungs, but behind the left ventricle, as in isolated mitral stenosis. Work has been done in patients with this valvular lesion, but the results in many may have been obscured by coexisting defects, such as mitral regurgitation, aortic stenosis, aortic insufficiency, and degenerative heart disease.[1,10-13] In the latter conditions left ventricular function may be impaired. Under such circumstances it would be difficult to evaluate changes in cardiodynamics after administration of digitalis since the effects of myocardial and mechanical factors may not be readily separable. Studies have also been performed in subjects with mitral stenosis and coexisting atrial fibrillation.[6,10,13-16] It is well established that digitalis increases vagotonia, thereby decreasing conduction through the bundle of His and increasing

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the refractory period of the A-V node, and also acts directly on the A-V node to inhibit conduction. These effects are most prominent in atrial fibrillation, resulting in an appreciable decrease in ventricular rate. In subjects with mitral stenosis this increase in diastolic time would allow greater emptying of the left atrium and a reduction in the rate of flow across the stenotic valve. Central vascular pressures behind the mitral valve may then decline to variable degrees.[16] Again, circulatory effects of the drug may be influenced by both the arrhythmia per se and the valvular stenosis.

It was considered, therefore, that a review of the effects of these drugs in patients with isolated mitral stenosis and regular sinus rhythm would be valuable. A study of patients with abnormal cardiodynamics due to a simple anatomic abnormality, in whom the number of variables are minimal, would allow for a more definitive evaluation of the effects of a drug on the circulatory system. In this case, mechanical hindrances to the passage of blood exist primarily at the mitral valve and secondarily in the pulmonary vascular bed. The only ventricle whose function may be impaired is the right ventricle.

Materials and methods

Seven female patients with mitral stenosis and regular sinus rhythm are the subjects of this study (Table I). They ranged in age from 17 to 48 years. The past histories of 4 patients (Cases 2-4, 7) included bouts of rheumatic fever; in 1 of them (Case 2) one episode occurred 7 months previously, but lasted only 2 to 3 weeks. All subjects complained of effort dyspnea. In 4 patients (Cases 3, 4, 6, 7), dyspnea began 8 to 15 years ago and became increasingly severe during the past 1 to 2 years. In 3 subjects (Cases 1, 2, 5), effort dyspnea of mild to moderate degrees occurred 1, 7, and 24 months, respectively, before the present studies. In 6 patients (Cases 2-7), orthopnea and bouts of nocturnal dyspnea were present for 7 months to 5 years. In 3 patients (Cases 2, 5, 7), slight ankle edema occurred 1 to 2 years previously, but disappeared after mercurial diuretic therapy. In another patient (Case 4), ankle edema began 4 years ago and, despite diuretic therapy, progressed in extent and severity. Physical examinations, chest x-ray films, and electrocardiograms gave the following pertinent findings: murmurs characteristic of mitral stenosis (Cases 1-7); soft, early systolic apical murmur (Case 5); murmurs suggesting tricuspid regurgitation (Cases 4, 7); peripheral edema (ankle, sacral) (Case 4); ascites (Case 4); distended neck veins (Cases 4 and 7); hepatomegaly (Cases 4 and 5); enlarged pulmonary arterial segments (slight in Cases 2 and 3, moderate in Cases 1, 6, and 7, marked in Cases 4 and 5); accentuation of peripheral pulmonary vascular markings (Cases 1-7); left atrial enlargement (slight in Case 2, moderate in Cases 1, 3, 5, 6, 7, marked in Case 4); right ventricular hypertrophy and enlargement (moderate in Cases 1, 3, 6, and 7, marked in Cases 4 and 5); right atrial enlargement (Cases 4, 5, and 7).

Body temperatures and acute phase reactants were normal in all subjects. Restriction of dietary salt was maintained in Cases 1 and 4 to 7. Several patients (Cases 4-7) had received mercurial injections during their previous illnesses. In Cases 1, 4, 5, and 7, digitalis therapy had been maintained in the past; however, no patient received this therapy for at least 3 weeks prior to these studies.

The presence of severe mitral stenosis (mitral valve area less than 1.0 $cm.^2$) was later confirmed by surgical exploration in 3 patients (Cases 3, 5, 6). In 1 patient (Case 4), mitral commissurotomy (valve area less than 1.0 $cm.^2$) had been performed 3 years prior to the present study. However, there was no change in the clinical state, and it was assumed that severe mitral stenosis persisted. Two patients (Cases 1, 7) refused to undergo operation. In 1 patient (Case 2), physiologic studies (vide infra) suggested that the mitral stenosis was mild; operation, therefore, was not recommended.

The patients were hospitalized and were semiambulatory or restricted to bed according to their functional capacities. They were observed for 10 to 14 days, during which time routine clinical observations were made and pertinent laboratory data obtained.

Physiologic studies of cardiovascular hemodynamics by the standard technique of right heart catheterization were then per-

formed (Tables IIA and IIB). The patients were in the recumbent positions and were not given premedication. Duplicate measurements of cardiac output (direct Fick) were made in the resting state. Oxygen consumption was obtained from analysis* of expired air collected in a Tissot spirometer during 3 minutes of quiet breathing. Samples of blood were obtained from the pulmonary and brachial arteries during the time of collection of expired air and were analyzed by the method of Van Slyke and Neill.[18] Multiple pressures were obtained with the use of Statham strain-gauge transducers and recorded on a multichannel oscillographic photographic recorder. Mean pressures were obtained by electrical integration of the pressure pulses. The point of zero reference for measurement of intracardiac pressures was taken at 5 cm. below the angle of Louis. Total pulmonary vascular, pulmonary "arteriolar," and total peripheral arterial resistances were calculated according to standard formulae (Poiseuille). Resistance is expressed as dynes /sec./cm.$^{-5}$ by the use of conversion factors.† Since measurements of flow, pressure, and resistance did not vary significantly during the control periods, only average values are tabulated (Tables IIA and IIB).

Lanatoside-C, 1.2 to 1.4 mg., was then injected directly into the pulmonary artery through the catheter over a period of 2 to 3 minutes. Pressures were measured at frequent intervals during the next 120 minutes. Cardiac outputs (direct Fick) were determined at least twice in all but 1 case (determined once at 90 minutes in Case 2) from 30 to 90 minutes after administration of the drug. Vascular resistances were calculated as described above. For the sake of brevity, only those parameters of cardiovascular dynamics which were measured at or closest to 10, 30, 60, and 90 minutes after administration of the drug are tabulated (Tables IIA and IIB). Because the data obtained after 90 minutes were similar to those obtained at 90 minutes, they are omitted from the tabulations. Other effects of the drug which may have occurred are described in the text.

Changes in cardiovascular hemodynamics as a result of administration of the drug were evaluated in terms of statistical probabilities. In order to determine whether these changes may have been due to chance variations, or to the action of an introduced variable (lanatoside-C in this study), an analysis was made of 29 consecutive right heart catheterizations performed in this laboratory in adults with various types of heart disease and with varying degrees of congestive failure. In each of these studies, at least 2 control determinations of "resting" cardiac output (direct Fick), multiple measurements of pressure, and calculations of resistance were performed at intervals of 22 to 143 minutes (average, 41 minutes), while the patients' states were considered to be constant. Chance or expected variations in terms of 95 per cent confidence limits (2 standard deviations from the mean variation) were established on this basis for the various measures of cardiovascular hemodynamics. A wide range of abnormalities in cardiodynamics was present in this control group, as would be expected in any series of patients with heart disease and congestive failure. It was thought, therefore, that greater reliability in an evaluation of the results would exist if these confidence limits were expressed in terms of percentage variations rather than changes in absolute values. Two exceptions are pulmonary "wedge" and right ventricular end-diastolic pressures. These parameters are expressed in terms of absolute changes because only minimal variations usually occur during a "resting" state, and because small variations in their usually low numerical values frequently result in inordinately high percentage changes.

Changes in cardiovascular dynamics in the present series of 7 patients who received lanatoside-C were then evaluated in terms of statistical significance at the 5 per cent level. Changes that were considered to be statistically significant are appropriately indicated in Tables IIA and IIB and in the discussion of the results.

Results

Control data (Tables IIA and IIB). Pulmonary hypertension was present in 6 of the 7 patients. It was mild in 2 patients (Cases 1, 3), moderate in 2 (Cases 5, 6), and moderate to severe in 2 (Cases 4, 7).

*Scholander gas analyzer.[17]

†1,332 = conversion factor from mm. Hg to dynes/cm.$^{-5}$.

Table I. Clinical status of patients at time of physiologic studies

Case	*F.C.*	*Dyspnea**	*Orthopnea*	*Neck vein distention (Gatch)*	*Liver size†*	*Peripheral edema‡*	*Pulmonary vascular congestion (x-ray)*	*Cardiac chamber enlargement*	*Electrocardiogram*	*Previous therapy*
1. Female Age 17 yr.	II	Moderate	None	None	Normal	None	Moderate	LA—moderate RV—moderate	Atrial hypertrophy; RVH	Low-salt diet (3.0-4.0 Gm. daily)
2. Female Age 29 yr.	II	Mild	2-pillow	None	Normal	None	Slight	LA—slight	Atrial hypertrophy; RAD	None
3. Female Age 29 yr.	II	Moderate	2-pillow	None	Normal	None	Slight	LA—moderate	Normal	None
4. Female Age 32 yr.	IV	Severe	3-pillow	90°	5	Marked	Marked	LA—marked RV—marked RA—marked	Atrial hypertrophy; RVH	Salt-free diet; frequent mercurial injections
5. Female Age 33 yr.	III	Moderate	2-pillow	None	1	None	Moderate	LA—moderate RV—marked RA—moderate	Atrial hypertrophy; RVH	Salt-free diet; frequent mercurial injections
6. Female Age 48 yr.	III	Moderate	3-pillow	None	Normal	None	Moderate	LA—moderate RV—moderate	Atrial hypertrophy; RVH	Salt-free diet; occasional mercurial injections
7. Female Age 48 yr.	II	Moderate	2-pillow	45°	Normal	None	Moderate	LA—moderate RV—moderate RA—moderate	Atrial hypertrophy; RVH	Low-salt diet (3.0—4.0 Gm. daily); occasional mercurial injections

F.C.: Functional classification (New York Heart Association).
*Severe if at rest, moderate if during mild effort, and slight if only during moderate effort.
†Measured as fingerbreadths below right costal margin.
‡Marked if involving more than lower extremities (presacral, abdominal wall); slight if involving ankles.
LA: Left atrium. RV: Right ventricle. RA: Right atrium. RVH: Right ventricular hypertrophy. RAD: Right axis deviation.

Table IIA. *Cardiovascular hemodynamics before and after the administration of lanatoside-C*

Case	*Lanatoside-C (mg.)*	*T*	*Heart rate (beats/min.)*	*Oxygen consumption (c.c./min./M.²)*	*A-V O_2 difference (c.c. %)*	*Cardiac index (L./min./M.²)*	*Stroke volume (c.c./beat)*	*Systemic arterial O_2 saturation (%)*
1.		Control	68	128	5.3	2.40	50	94
		10 min.	62	—	—	—	—	—
	1.2	30 min.	60*	—	—	—	—	—
		60 min.	60*	148*	4.7	3.15*	74*	91
		90 min.	65	142	4.9	2.90	63	90
2.		Control	87	93	6.0	1.55	29	95
		10 min.	80	—	—	—	—	—
	1.4	30 min.	90	—	—	—	—	—
		60 min.	75*	—	4.9	—	—	94
		90 min.	75*	84	6.0	1.40	31	94
3.		Control	90	95	4.9	1.94	33	96
		10 min.	75*	—	—	—	—	—
	1.4	30 min.	72*	101	4.7	2.15	43	96
		60 min.	70*	101	4.9	2.06	47*	95
		90 min.	67*	93	5.0	1.86	44*	94
4.		Control	95	137	10.1	1.35	19	89
		10 min.	90	—	—	—	—	—
	1.2	30 min.	88	—	—	—	—	—
		60 min.	86	151	9.2	1.64	26*	92
		90 min.	90	152	9.3	1.64	25*	92
5.		Control	100	122	5.7	2.14	27	89
		10 min.	83*	—	—	—	—	—
	1.4	30 min.	60*	120	4.8	2.50	53*	91
		60 min.	73*	138	5.0	2.76*	49*	91
		90 min.	68*	—	—	—	—	91
6.		Control	76	138	5.6	2.46	60	93
		10 min.	60*	—	—	—	—	—
	1.2	30 min.	58*	—	—	—	—	—
		60 min.	70	154	5.2	3.00	80*	91
		90 min.	60*	138	5.0	2.76	86*	94
7.		Control	95	125	6.0	2.08	37	94
		10 min.	80*	—	—	—	—	—
	1.4	30 min.	80*	117	5.5	2.13	45	96
		60 min.	93	114	5.6	2.04	37	96
		90 min.	90	112	6.0	1.87	35	96

Under T, Control denotes the period prior to the administration of lanatoside-C (average values are tabulated). This is followed by the periods 10, 30, 60, and 90 minutes after administration of the drug. The tabulated data are those measured at or closest to these time periods.

*Denotes those values which are statistically significantly different (> 2 standard deviations) from control values.

Pulmonary "wedge" pressures were measured during the control period in 5 patients; they were elevated in all but 1 of them (Case 2). Right ventricular end-diastolic pressures were normal in 3 patients (Cases 1, 2, 6), slightly elevated in 3 (Cases 3, 5, 7), and markedly elevated in 1 (Case 4). Systemic arterial pressures were normal in each subject.

Cardiac outputs were low in all 7 patients. Arterial-mixed venous oxygen differences were elevated in all but 1 patient (Case 3). In 2 patients (Cases 4, 5), systemic arterial oxygen saturations were slightly diminished.

Total peripheral resistances were moderately elevated in all subjects. Total pulmonary vascular resistances were elevated in all patients, slightly in 2 (Cases

1, 2), moderately in 2 (Cases 3, 4), considerably in 3 (Cases 4-6). Pulmonary "arteriolar" resistances calculated during the control periods in 5 patients were found to be slightly abnormal in 3 (Cases 1-3), and moderately elevated in 2 (Cases 4, 5).

Cardiovascular dynamics after the administration of lanatoside-C (*Tables IIA and IIB*). In 2 (Cases 2, 6) of the 7 subjects, lanatoside-C did not affect cardiovascular dynamics to any important degree. Significant reductions in heart rates occurred

Table IIB. *Cardiovascular hemodynamics before and after the administration of lanatoside-C*

Case	T	Pressure (mm. Hg)								Resistance (dynes/sec./cm.$^{-5}$)		
		Peripheral artery			Pulmonary artery			Pulmonary "wedge"	Right Ventricular (D†)	Total systemic	Total pulmonary vascular	Pulmonary "arteriolar"
		S	D	M	S	D	M	M				
1.	Control	120	69	86	41	19	25	15	1	2,040	575	210
	10 min.	—	—	—	39	19	26	—	2	—	—	—
	30 min.	116	63	84	47	21	29	—	2	—	—	—
	60 min.	125	68	84	50*	19	30	17	1	1,510*	520	198
	90 min.	123	68	85	48	20	30	17	0	1,660	605	272
2.	Control	110	61	77	20	8	12	7	3	2,430	370	150
	10 min.	120	59	79	18	6	10	—	1	—	—	—
	30 min.	116	57	82	20	8	11	—	1	—	—	—
	60 min.	116	51	68	20	7	11	—	3	—	—	—
	90 min.	102	55	69	20	7	11	5	3	2,410	385	210
3.	Control	107	61	77	37	20	27	21	6	2,000	730	220
	10 min.	116	69	85	41	18	22	—	7	—	—	—
	30 min.	105	66	80	37	17	22	—	5	1,880	520*	—
	60 min.	101	56	75	33	14*	21*	15*	4	1,840	520*	290
	90 min.	102	57	74	36	14*	21*	15*	8	2,010	680	270
4.	Control	93	66	73	96	40	59	48	22	3,250	2,660	665
	10 min.	103	73	80	114*	38	59	—	24	—	—	—
	30 min.	—	—	—	114*	40	57	—	23	—	—	—
	60 min.	100	62	72	120*	41	61	52	21	2,590*	2,190	325
	90 min.	120*	70	80	120*	42	67	—	18*	2,880	2,410	—
5.	Control	92	61	73	74	35	50	30	8	2,120	1,480	570
	10 min.	123*	68	86*	65	29	41	—	3*	—	—	—
	30 min.	118*	59	79	50*	20*	30*	16*	3*	1,980	750*	380
	60 min.	112*	56	78	64	22*	33*	—	1*	1,760	700*	—
	90 min.	112*	56	74	60	20*	32*	14*	0*	—	—	—
6.	Control	134	77	94	75	23	42	—	5	1,640	734	—
	10 min.	158*	84	109*	65	17	34	—	4	—	—	—
	30 min.	150	80	105*	83	22	40	—	3	—	—	—
	60 min.	146	77	100	78	23	40	17	4	1,340	570	330
	90 min.	132	62*	84	78	22	39	18	3	1,350	610	330
7.	Control	136	78	104	125	41	74	—	6	2,400	1,700	—
	10 min.	153	71	104	109	28*	53*	—	5	—	—	—
	30 min.	121	58*	82*	110	37	62	—	5	2,300	1,380	—
	60 min.	123	75	103	111	39	58*	—	2*	2,390	1,350	—
	90 min.	124	71	90*	125	38	63	—	2*	2,280	1,600	—

T: Same as in Table IIA.
*Denotes those values which are statistically significantly different (> 2 standard deviations) from control values.
†End-diastolic.

60 and 10 minutes after administration of the drug and continued for the remainder of the studies. In Case 6, stroke volumes rose.

In the other 5 patients (Cases 1, 3-5, 7), important changes in cardiovascular hemodynamics occurred after administration of the drug. In Cases 3, 5, 7, pulmonary arterial diastolic and mean pressures decreased significantly. In Case 7 this response was transient at 10 and 60 minutes. In Cases 3 and 5 these changes occurred at 60 and 30 minutes, respectively, and continued for the remainder of the study. In 2 patients (Cases 3 and 5), pulmonary "wedge" pressures were measured before and after administration of the drug; significant reductions were noted concomitant with the changes in pulmonary arterial pressures. In Case 5 a transient decrease in pulmonary arterial systolic pressure occurred at 30 minutes. In each of these 3 patients, significant decreases in heart rates occurred 10 minutes after administration of the drug. In 2 of them (Cases 3 and 5) the changes in heart rate persisted; in the other (Case 7) the heart rate returned to control levels at 60 minutes. Stroke volumes increased significantly in Cases 3 and 5. Only in the latter case did stroke volume increase enough to effect a significant increase in cardiac output. In these 3 subjects, control right ventricular end-diastolic pressures were elevated. In Case 3 no changes occurred after administration of the drug. In Cases 5 and 7, right ventricular diastolic pressure decreased significantly and to normal at 10 and 60 minutes, respectively, and remained at these levels or lower for the duration of the studies. Pulmonary vascular resistances did not change except in 1 subject (Case 5) in whom there was a moderate reduction in total pulmonary vascular resistance.

In the other 2 (Cases 1, 4) of the 5 patients in whom important hemodynamic changes occurred after therapy with lanatoside-C there were significant increases in pulmonary arterial systolic pressures, but no changes in pulmonary arterial diastolic and mean pressures. In 1 subject (Case 4) this increase occurred at 10 minutes and remained at that level for the rest of the study. This was associated with significant increases in stroke volumes, and, at 90 minutes, with a definite reduction in right ventricular end-diastolic pressure. (The latter was abnormal during the control period.) Heart rate did not change. Cardiac output increased somewhat but not to a significant degree. In the other patient (Case 1), pulmonary arterial systolic pressure rose transiently at 60 minutes. This was associated with significant increases in stroke output, cardiac output, and oxygen consumption. It is not entirely certain that these effects were due to the glycoside. They may have been a consequence of a change in metabolic state, as indicated by the significant increase in oxygen consumption.

Additional information. Systemic arterial pressures increased in some subjects (Cases 4-7). In 1 subject (Case 5), systolic pressure increased 10 minutes after administration of the drug and continued to be elevated for the remainder of the study. In the other 3 subjects the increases were transient and inconstant and bore no relationship to changes in other parameters of cardiovascular function.

Systemic arterial oxygen saturations did not change after drug therapy.

There were no changes in signs or symptoms as related to the cardiovascular system after administration of lanatoside-C. In Case 2, slight nausea occurred after 23 minutes, and in Case 7, periodic first-degree A-V block and intermittent shifting atrial pacemaker occurred after 30 minutes.

Discussion

Changes in cardiodynamics after the administration of lanatoside-C in the subjects of this study were variable. However, the data do indicate certain patterns, the formation of which depend on the actions of the drug, to a greater or lesser degree, upon various components of the cardiovascular system, and also upon the physiologic status of the patient at the time of the study.

One pattern is illustrated by the results in Case 4. In this subject there was an early rise in pulmonary arterial systolic pressure accompanied by an increase in stroke output and later by a decrease in right ventricular end-diastolic pressure. Pulmonary arterial mean and diastolic pressures and pulmonary "wedge" pressure

did not change. Cardiac output rose somewhat but not to a significant degree. Heart rate did not change. These changes are generally similar to those which follow the administration of cardiac glycosides in chronic cor pulmonale.[2] After drug therapy the decrease in filling pressure and, presumably, in residual blood volume of the right ventricle indicates better emptying of this chamber as a consequence of improvement in its function. The increase in stroke output takes place in a pulmonary vascular bed from which the outflow is obstructed. In chronic cor pulmonale the obstruction is at the pulmonary precapillary area, whereas in mitral stenosis the obstruction is primarily at the mitral valve and, secondarily, at the pulmonary precapillary area. (Pulmonary "arteriolar" resistance was markedly elevated in our case.) An increase in flow through an area of increased resistance is accompanied by a rise in pressure proximal to the obstruction. This would explain the increases in pulmonary arterial systolic pressures in both conditions.

Another pattern is illustrated by Cases 3, 5, and 7. In this group of patients the most consistent changes in the lesser circulation after administration of the drug were declines in pulmonary arterial diastolic and mean pressures. Various possibilities may be suggested to account for this occurrence. A reduction in pulmonary "arteriolar" resistance may offer less obstruction to outflow from the right ventricle and, thereby, allow a reduction in the pressure head relative to this flow. Pulmonary arterial systolic pressure should then decrease unless there is an appreciable increase in blood flow. Blood flow did not increase significantly in 2 of these 3 subjects, and pulmonary arterial systolic pressures did not show consistent changes. In addition, calculated pulmonary "arteriolar" resistances did not change (Cases 3 and 5).

Another factor which could have caused a reduction in pulmonary arterial pressures is dilatation of the pulmonary vascular bed. It has been suggested that digitalis preparations may directly influence certain vascular beds, such as to produce systemic venous pooling[5,20,21] and to increase total peripheral arterial resistance.[8,22] In the human subject with heart failure, however, such effects are relatively minor, and are overshadowed by other cardiovascular changes. There is no evidence to date that digitalis preparations cause a dilatation of the pulmonary vascular bed. Although this possibility cannot be definitely eliminated from consideration, the unlikelihood of its occurrence and the absence of supporting data in the literature suggest that its role, i.e., a change in distensibility properties of the pulmonary vasculature, in contributing to the changes noted in this study is negligible.

A decrease in right ventricular stroke output may contribute to a decrease in pulmonary arterial pressure. However, this was not a factor in this study because stroke output did not fall; in fact, it increased in Cases 5 and 7.

Decreases in pulmonary blood volumes (albeit not supported by direct measurements) could have been responsible for the declines in pulmonary diastolic and mean pressures, as well as for the declines in pulmonary "wedge" pressures. Other investigators have demonstrated that the relationship between pulmonary blood volume and pulmonary vascular pressures is dependent upon the volume-elasticity properties of the pulmonary vasculature.[23-25] The pressure-volume curves of this vascular bed are characterized by upward convexities when pressure is plotted on the vertical axis. Thus, at normal levels of pulmonary blood volume and pulmonary pressures, changes in volume produce minimal changes in pressure. As volume increases progressively, a point is reached at which pressure rises sharply. At elevated levels of pressure, small changes in volume may accomplish appreciable changes in pressure. The presence of pulmonary arterial and venous hypertension in our subjects probably indicates that pulmonary blood volume was initially increased to some degree. It then reasonably appears that, since other factors (see above) were constant, the changes in pressures after administration of the drug were due to changes in volumes.

It would be important to know how reductions in pulmonary blood volumes could have been produced in these subjects (Cases 3, 5, 7). Since falls in right ventricular output did not occur, improve-

ment in emptying of the left heart remains as the logical alternative. The mode by which the latter may have been accomplished is somewhat speculative but the data do permit reasonable conclusions. A positive inotropic effect of the digitalis preparation on a decompensated left ventricular myocardium is one possibility. Other workers[1,4,9,11] have demonstrated improvements in cardiac output and in pulmonary arterial pressures after the administration of a cardiac glycoside to patients with left ventricular failure. In human subjects without myocardial failure, however, these drugs do not influence pressures in the lesser circulation and either do not change or do cause a reduction in cardiac output.[3,6,8,13,26] It would have been valuable in this respect to measure left ventricular end-diastolic pressures in our subjects, since this would have given more direct indications of the function of the left ventricle. However, it was considered that prolonged catheterization of the left heart would incur excessive risk. Clinically, at least, there was no reason to suspect alteration in left ventricular function, although the possibility of the histologic stigmas of rheumatic myocarditis always exist. Certainly, the size of the left ventricle was normal as demonstrated by clinical examination (Cases 1-7) and at operation (Cases 3-6). In addition, in 2 (Cases 3 and 7) of these 3 patients (Cases 3, 5, 7), cardiac output did not change after drug therapy, an occurrence which is unusual when digitalis is administered to subjects with bona fide left ventricular failure.[1,4-6,9,11,13]

A more likely mechanism for the improvement in the emptying of the left heart is the reduction in ventricular rates. This occurred in each subject (Cases 3, 5, 7) in this group almost simultaneously with the changes in pulmonary arterial pressures. The influence of ventricular rate per se upon lesser circulatory pressures in mitral stenosis is well known.[16,19,27] The pressure gradient across the stenotic valve depends upon the flow across that valve. In mitral stenosis, this (diastolic) flow has the characteristics of a steady rate (rather than an accelerated rate in early diastole when the valves are normal). Thus, the diastolic period becomes an important determinant of the amount of blood which can leave the lungs and left atrium per unit time. Therefore, by the simple mechanism of ventricular bradycardia due to drug action on vagal centers and directly on cardiac conduction tissue, the period during which flow can occur across the stenotic mitral valve is increased, permitting a greater emptying of pulmonary (and, possibly, left atrial) vascular beds, a decrease in their blood volumes, and, thus, falls in pressures behind the valve. That the increases in stroke volumes in Cases 3 and 5 are secondary to this bradycardia rather than due to primary inotropic effects of the drug is suggested by the observations that (a) in Cases 3 and 7, cardiac outputs did not change (cardiac output usually increases concomitant with stroke output after digitalis therapy in myocardial failure, as described above), and (b) in Case 7, stroke output did not change although ventricular rate decreased, indicating that the latter may occur as a primary phenomenon.

The influence of ventricular rate upon pulmonary arterial pressures is further emphasized in Case 7. Drug-induced bradycardia occurred transiently at 10 and 30 minutes. This was associated with reductions in pulmonary arterial mean and diastolic pressures (at 10 minutes). A return of heart rates to control levels at 60 and 90 minutes led to a restoration of pulmonary pressures (at 90 minutes).

In these 3 subjects (Cases 3, 5, 7), right ventricular end-diastolic pressures were initially abnormal. In 2 (Cases 5, 7), lanatoside-C improved the function of the right ventricle, causing decreases in the filling pressures of the right heart to normal after 10 and 60 minutes, respectively.

A third pattern is represented by the other 3 cases (Cases 1, 2, 6). Significant reductions in ventricular rates occurred after administration of the drug, but there were no other important changes in cardiodynamics which could be attributed to the cardiac glycoside. It is not clear why bradycardia may permit decreases in pulmonary pressures in some cases and not in others. In 1 case (Case 6), right ventricular end-diastolic pressure which was abnormal during the control period did not change. Again, no explanation is apparent

for the improvement in function of the right ventricle in some instances and not in others. Perhaps the inability of the myocardium to respond because of pathologic factors is of some importance.

Other workers[8] have demonstrated that cardiac glycosides may increase systemic arterial pressure by affecting peripheral resistance. In Cases 4 to 6, increases in systemic arterial pressures did occur, but they were variable and followed no pattern, nor did they have any definite relationship with the other changes in cardiodynamics described above. Peripheral resistances did not change (Cases 5, 6) or actually decreased (Case 4). It appears that the effects of digitalis on peripheral resistance are minor in human congestive heart failure, and that the more important effects of this drug on cardiac function determine cardiodynamic events to a greater degree.

It appears, therefore, that the ultimate changes in cardiodynamics after the administration of digitalis in patients with mitral stenosis and regular rhythm depend upon the interaction of several factors. Improvement in right ventricular function results in increased output into a vascular bed from which outflow is obstructed and in which capacity may be restricted; right ventricular end-diastolic pressure tends to fall, cardiac output and stroke volume tend to rise, and pulmonary arterial systolic pressure tends to rise. Drug-induced bradycardia with its attendant increase in diastolic time may permit greater emptying of the pulmonary vascular bed across the narrowed valve area, which, in turn, may accomplish reductions in pulmonary arterial diastolic and mean pressures. Stroke volume may rise as a phenomenon secondary to the bradycardia. Cardiac output increased only in 1 subject (Case 5) who had improvement in right ventricular function. In our subjects, when both improvement in right ventricular function and bradycardia occurred at the same time, the latter appeared to exert the dominant influence upon pulmonary vascular pressures. In some subjects, right ventricular function may not improve, and bradycardia may not influence central vascular pressures. The effect of the drug on peripheral resistance was unimportant.

In the present discussion the concept of improvement in right ventricular function has been applied in a general manner. The data do not indicate the primary site of action of the drug, whether on the myocardium as a positive inotropic effect or on a peripheral venous vascular bed to reduce venous return, and, thereby, improve cardiac overstretch. The time relationships between cardiac output and pressures are not helpful, because the former was not measured earlier than 30 minutes after administration of the drug.

The clinical application of digitalis in patients with mitral stenosis and regular sinus rhythm may offer some benefit, although not so impressive as in patients with left ventricular decompensation. If a reduction in ventricular rate should occur, at least in the nonexercising state, a decrease in pulmonary blood volume and salutary falls in lesser circulatory pressures may result. If right ventricular failure exists, the drug may improve the function of the right ventricle. It has been stated[8] that an increase in the output of the right ventricle (as the function of this chamber improves) into a pulmonary vascular bed from which the outflow is obstructed may raise the pulmonary capillary hydrostatic pressure and produce pulmonary edema. The necessary prerequisite for this effect on cardiac output is a decompensated right ventricle. The latter is usually associated with an appreciable elevation in pulmonary "arteriolar" resistance. In this study, only 1 case (Case 4) illustrates this set of circumstances (in which the effects of increased flow upon pulmonary pressures were not overshadowed by bradycardia). In this subject, pulmonary "wedge" pressure, although markedly elevated initially, did not rise further. The pressure which rose as flow increased was that behind the pulmonary precapillary bed (pulmonary systolic pressure).

Summary

This study is concerned with the acute effects of intravenous lanatoside-C upon the cardiovascular dynamics of 7 female patients with mitral stenosis and regular sinus rhythm.

Control data revealed that pulmonary arterial hypertension of mild to severe degrees was present in 6 patients, pulmo-

nary "wedge" pressures were elevated in 4 of the 5 patients in whom they were measured, cardiac outputs were depressed in all patients, and right ventricular decompensation as indicated by an elevation in end-diastolic pressure was present in 4 patients. Pulmonary vascular resistances were elevated to variable degrees in all patients.

The cardiodynamic responses to the administration of lanatoside-C were distinguished by 3 patterns. In one pattern, improvement in right ventricular function (abnormal initially) resulted in an increased output into a vascular bed from which the outflow was obstructed. Right ventricular end-diastolic pressure fell, cardiac output and stroke volume rose, and pulmonary arterial systolic pressure rose. A second pattern demonstrated the salutary effects of bradycardia with its attendant increase in diastolic time. This permitted greater emptying of the pulmonary vascular bed, which, in turn, caused reductions in pulmonary arterial diastolic and mean pressures and pulmonary "wedge" pressure. Stroke volumes increased as phenomena secondary to the bradycardias. Cardiac output increased in that subject who had improvement in right ventricular function. When both improvement in right ventricular function and bradycardia occurred in the same subject, the latter exerted the dominant influence upon pulmonary vascular pressures. The third pattern was characterized by an absence of hemodynamic changes after administration of lanatoside-C.

The possible benefits which the administration of digitalis may exercise in patients with mitral stenosis and regular sinus rhythm are discussed.

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Sinus arrhythmia in rheumatic fever

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One of the first descriptions of sinus arrhythmia was by Ludwig[1] in 1847. In 1860, Einbrodt,[2] a pupil of Ludwig, suggested that the cause of sinus arrhythmia was an alteration in the tone of the cardio-inhibitory center. Brodie and Russell[3] agreed with Einbrodt, but Hooker[4] showed that this explanation was inadequate because they were able to produce reflex changes in the heart rate via the accelerator nerves after the vagi had been cut.

The stimulus which changes the tone of the cardio-regulatory centers is not known for certain. Among the theories advanced have been chemical changes in the blood,[5] the Hering-Bruer reflex,[6] overflow of stimuli from the respiratory center,[7] stimuli from muscles of respiration,[8] and stimuli from rise of pressure in the right auricle and great veins.[9,10] However, as Landtman[11] says, "It is possible that several of these factors contribute."

In 1902, Mackenzie[12] separated sinus arrhythmia from other causes of irregular action of the heart and called it the "youthful type of irregularity." He noted that it occurred especially between the years of 8 and 15. He pointed out that after rheumatic fever it was commonly taken to be a grave sign, but he had observed that the presence of sinus arrhythmia indicated the absence of heart involvement. He said that he had never seen sinus arrhythmia in acute rheumatic fever nor in progressive rheumatic heart disease, and that its presence in old valvular affections suggested that there was no active carditis.[13]

Parkinson and Hope Gosse[14] stated that the presence of sinus arrhythmia did not indicate that the heart had escaped involvement, recent or remote. McCrudden[15] observed that sinus arrhythmia occurred in rheumatic fever but that its absence carried a poor prognosis. Luisada[16] said that severe sinus arrhythmia is sometimes caused by the rheumatic process. Lewis[17] commented that it is especially frequent in patients with rheumatic heart disease when they are taking digitalis. Wood[18] stated that, although it is normal, it may occur in any form of heart disease, and Myers[19] pointed out that it occurs in children with acute rheumatic carditis.

Nordenfelt[20] compared the degree of sinus arrhythmia in normal children with that in 126 "sick" children. He found that the values were similar in both groups, but unfortunately his group of sick children included children with endocarditis

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due to causes other than rheumatic fever, such as respiratory infection with heart murmurs; the group with disease was therefore not homogeneous. Landtman[11] made a comprehensive study of the degree of sinus arrhythmia in a group of normal children and in a group with active rheumatic carditis, and found less sinus arrhythmia in the group with disease.

We felt that, although adequate data were available on sinus arrhythmia in rheumatic carditis,[11] it was worth while to collect further data on patients with initial attacks (with and without carditis) and on those with recurrences of rheumatic fever.

Plan of study

Material. Sinus arrhythmia was studied in two series of children. The first group consisted of children with an acute initial attack of rheumatic fever; these were studied on admission and on discharge. The second group consisted of children admitted with a recurrent attack of rheumatic fever. Our material was comprised of patients in the cooperative trial of ACTH, cortisone, and aspirin,[21] and those in a current therapeutic trial.[22] All patients had been in the House of the Good Samaritan, and the age limit was 17 years. After the exclusion of patients in whom the P-R interval varied or was prolonged, those in whom the rhythm did not originate in the sinus node, and those in whom electrocardiograms were not available, there were 135 patients for the present study, of whom 85 were suffering their initial attack. A group of 93 children with normal hearts was used as controls.[23] These were patients in the Children's Medical Center who had not had rheumatic fever and who were free of cardiac disorders and infection. Their cardiovascular systems had been examined by a cardiologist and were found to be entirely normal. Patients with an initial attack of rheumatic fever were divided into those without carditis (normal-heart rheumatic group, 27 patients) and those with carditis (carditis group, 58 patients).

Carditis was considered to be present if any of the following conditions existed: development of an organic apical systolic murmur or an aortic diastolic murmur under acceptable observation; pericarditis, revealed by a definite friction rub or by pericardial effusion; or congestive failure. Congestive failure was always accompanied by either of the other two conditions.

Age and sex distribution are shown in Table I. There was a greater proportion of children under 6 years of age in the control group than in any of the study groups, and a greater proportion of children over 10 years of age in the normal-heart group. About one and one-half times more boys were present in the control and normal-heart groups, whereas more girls were present in the carditis group. The recurrence group is described later.

Method. We examined the electrocardiogram taken with three standard leads, each usually comprising six complexes. The maximum and minimum R-R intervals were measured to the nearest 0.5 mm., and the average of six R-R intervals was measured. The degree of sinus arrhythmia (frequency index) was then calculated, using the method described by Schlomka and Reindell.[24] Thus, the shortest R-R interval was subtracted from the longest R-R interval, and the result was divided by the mean of six R-R intervals and multiplied by 100. This method has been used because it takes into consideration the heart rate and because it expresses sinus arrhythmia quantitatively.

Table I. *Age and sex*

Group	*Age (years)*			*Total*	*Boys*	*Girls*
	2–5	6–10	11–17			
Control	25	49	19	93	56	37
Rheumatic fever:						
"Normal" heart	0	15	12	27	17	10
Carditis	6	36	16	58	24	34

Table II. *Frequency index on admission*

Group	*Number*	*Frequency index*	*Mean heart rate*
Control	93	22.3 ± 1.4	93
Rheumatic fever:			
"Normal" heart	27	18.9 ± 3.0	96
Carditis	58	14.6 ± 2.0	116

Results

On admission. Table II shows the average frequency index on admission. The control and normal-heart groups had similar frequency indices, with means of 22.3 and 18.9 and average heart rates of 93 and 96, respectively. The mean frequency index of 14.6 in the carditis group was, however, less, and the difference between this and the figure for the control group was highly significant ($p = <.01>.001$). The carditis group, however, had a higher average heart rate, and Table III shows that in patients whose rates were less than 100 per minute the frequency indices were similar in all groups. Table IV shows the frequency indices of patients whose heart rates were 100 per minute or more. This showed that at these faster rates the frequency indices of both the normal-heart and carditis groups were significantly lower than that of the control group ($p = <.01>.001$).

On discharge. The change in the frequency index by the time of discharge was next investigated (Table V). The normal-heart group showed a significant decrease in the index as compared with that at the time of admission ($p = <.05>.02$), but the difference in the frequency index of the carditis group between admission and discharge was not significant at the 5 per cent level. Both groups showed very similar degrees of sinus arrhythmia at the time of discharge.

Recurrences

The group of 50 children suffering recurrences has been analyzed separately. The age and sex of these children are shown in Table VI. They were older than those with an initial attack; 70 per cent were more than 10 years of age as compared with 33 per cent of those having an initial attack. Duration of disease before admission was difficult to determine because in some patients the onset was insidious, but in general it was about 3 weeks longer than in those with an initial attack.

Table VII shows the frequency index in the recurrence group at the time of admission. Values for the carditis group on admission and on discharge are included in the table for comparison. The difference in frequency indices between the two groups on admission was highly significant ($p = <.001$), but the difference between the recurrence group on admission and the carditis group on discharge was small and not significant ($p = <0.1> .05$). There was a similar small difference between the recurrence group on admission and the normal-heart group on discharge.

The recurrence group was divided into two groups on the basis of heart rate, like the grouping for those with an initial attack, and Table VIII shows the results. At slow rates there was a highly significant decrease in sinus arrhythmia in the recurrence group as compared with findings in the control or normal-heart or carditis groups on admission. At the faster rates, although the difference between the recurrence and carditis groups was less marked, it was significant at about the 5 per cent level ($p = <.05> .02$), and this in spite of the presence of an average faster heart rate in the carditis group.

Discussion

Our results (Table II) suggest that sinus arrhythmia is significantly less marked in patients with an initial attack of rheumatic fever with carditis than in our controls. There were differences between those patients with carditis and those without, and between controls and those without carditis, but these differences were not large. The average heart rates in the control and normal-heart groups were similar (93 and 96, respectively), but in the car-

Table III. *Frequency index on admission in patients with heart rates under 100 per minute*

Group	*Number*	*Frequency index*	*Mean heart rate*
Control	62	26.6 ± 1.7	82
Rheumatic fever:			
"Normal" heart	15	28.8	81
Carditis	17	33.9 ± 4.0	83

Table IV. *Frequency index on admission in patients with heart rates of 100 per minute or more*

Group	*Number*	*Frequency index*	*Mean heart rate*
Control	31	13.5 ± 1.5	116
Rheumatic fever:			
"Normal" heart	12	6.6 ± 1.4	115
Carditis	41	6.8 ± 1.6	127

Table V. *Frequency index on admission and on discharge in patients with rheumatic fever*

Group	*Number*	*On admission*		*On discharge*	
		Index	*Mean heart rate*	*Index*	*Mean heart rate*
"Normal" heart	27	18.9 ± 3.0	96	10.4 ± 2.2	91
Carditis	58	14.6 ± 2.0	116	10.6 ± 2.0	99

Table VI. *Recurrence group: age and sex*

Number	*Age (years)*		*Boys*	*Girls*
	6–10	11–17		
50	15	35	23	27

Table VII. *Frequency index in recurrence group on admission and in carditis group on admission and on discharge*

Group	*Number*	*Frequency index*	*Heart rate*
Recurrence	50	6.3 ± 1.2	98
Carditis, on admission	58	14.6 ± 2.1	116
Carditis, on discharge	58	10.6 ± 2.0	99

Table VIII. *Frequency index in recurrence and carditis groups at heart rates of under 100 per minute and 100 per minute and over*

Group	*Number*	*Under 100 per minute*	*Mean heart rate*	*Number*	*100 per minute and over*	*Mean heart rate*
Recurrence	26	9.2 ± 2.0	84	24	3.3 ± 0.6	114
Carditis	17	33.9 ± 4.0	83	41	6.8 ± 1.6	127

Table IX. *Frequency index on admission: patients 6-10 years old*

Group	*Number*	*Frequency index*	*Heart rate*
Controls	49	25.3	89
Rheumatic fever:			
"Normal" hearts	15	22.1	91
Carditis	36	14	115
Landtman[11] (1947)			
Controls	50	13.5	89
Carditis	50	6.1	97

ditis group the rate was 116 per minute. In order, therefore, to eliminate the variation of heart rates, only patients with rates of less than 100 per minute were included in Table III. These results suggested that the lower frequency index in patients with carditis was due to the higher average heart rates in this group. However, when the index at fast rates was investigated (Table IV), a significant decrease was found in the normal-heart and carditis groups as compared with the control group. It is possible, therefore, that the two heart-rate groups did not behave uniformly, and that there was a slow-rate group which did not differ from controls, and a fast-rate group in which sinus arrhythmia was less than that in controls. Unfortunately, the carditis group (Table IV) had a faster average heart rate (127) than did the control or normal-heart groups, so that it is not certain how big a part tachycardia was playing, but it is interesting that at fast rates the normal-heart group behaved in the same way as the carditis group, having a lower frequency index than controls at almost identical heart rates.

The changes in the frequency index by the time of discharge were also interesting. The most significant change was in the normal-heart group, which showed a marked drop in the frequency index. This resulted in both the normal-heart and carditis groups having very similar indices at the time of discharge.

Our results on admission were similar to those of Landtman,[11] who showed that patients with rheumatic heart disease had less sinus arrhythmia than did a group of controls. Since age influences sinus arrhythmia, we have included in Table IX only those patients who were between 6 and 10 years of age, so that Landtman's figures can be compared with ours. It can be seen that the differences between the control and carditis groups were similar to those of Landtman's, but the figures themselves show a marked difference. In general, the values, both for our control and carditis groups, were about twice those of Landtman's. It is possible that some of this difference in the carditis group was due to the fact that in our analysis we separated those patients who were suffering an initial attack of rheumatic fever from those who had had more than one attack, but this does not account for the difference between the control groups, wherein the average heart rates were identical, 89 per minute. However, Schlomka[25] and Nordenfelt[20] found a frequency index of about 17 in a group of children who ranged in age from 6 to 15 years, and this figure is similar to the 23 for our controls who were 6 to 17 years of age. Thus, there has been considerable variation in the frequency indices in control groups previously reported on.

When we investigated the recurrence group, we found that sinus arrhythmia was less marked than in those patients who were suffering an initial attack. However, by the time of discharge the frequency index of the latter group was very similar to that of the recurrence group at the time of admission. We are unable to explain this decrease at the time of discharge, nor the low frequency index in the recurrence group on admission, but these changes would be in keeping with a theory suggested by Weber[26] that the sinus node contains a "Kontraktionssubstanz" necessary for its normal function, and that this "substance" might be injured by the rheumatic process.[11]

We would like to postulate tentatively that the node is damaged by the initial

rheumatic attack and that the injury persists, as shown by the decreased sinus arrhythmia at the time of discharge and a similar low frequency index in patients with recurrences at the time of their admission.

Summary

1. The degree (frequency index) of sinus arrhythmia was investigated in children suffering an initial attack of rheumatic fever (with and without carditis), in children with a recurrent attack, and in children with normal hearts who served as controls.

2. At slow heart rates (less than 100 per minute) there was no difference between the control, normal-heart, and carditis groups at the time of admission, but a highly significant decrease was observed in the recurrence group.

3. At fast heart rates (100 per minute and more) both the normal-heart and carditis groups on admission showed a significant decrease in sinus arrhythmia as compared with the control group, and the recurrence group showed a significant decrease as compared with the normal-heart and carditis groups.

4. At the time of discharge, the normal-heart and carditis groups showed similar values; the values for the former had decreased more than had those for the latter, as compared with the admission values.

5. It is suggested that the fall in sinus arrhythmia observed between admission and discharge and the low-frequency index of sinus arrhythmia in the recurrence group may be due to permanent damage to the sinus node by the rheumatic process.

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Essential hypertension with an elevated noradrenaline excretion

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Shortly after noradrenaline was discovered as the neurohormone of the sympathetic nerves,[1] a number of papers appeared postulating a possible correlation between essential hypertension and an increase in the output of noradrenaline.[2-4] In general, these papers did not demonstrate any significant relationship between the output of noradrenaline and the hypertension. However, von Euler and associates[4] did show that 16.4 per cent of their hypertensive patients had an abnormally high output of noradrenaline, and Holtz and associates[2] believed that the urine from hypertensive patients showed a somewhat higher content of noradrenaline than did that from normal subjects.

When one considers all of the many possible causes of essential hypertension and the relationship of the sympathetic nerves to the control of human blood vessels,[5,6] it certainly seems reasonable to assume that, at least in some hypertensive patients, the etiology is directly related to an increase in the activity of the sympathetic nerves. The purpose of this paper is to demonstrate the possibility of such a relationship.

Methods

Determinations of urinary catecholamines were made on approximately 500 patients with an elevated systolic and diastolic blood pressure; the range of elevation of the blood pressure and the intensity of the illness varied greatly. Of the 500 patients, 2 subjects with an elevated blood pressure and an increase in the urinary output of noradrenaline were selected for a more thorough evaluation.

1. General. The 24-hour urines were collected, acidified, and assayed for adrenaline and noradrenaline. Collections were made at the time of admission, at various other times during hospitalization, and after discharge.

2. Preparation of urine extract. The urine was hydrolyzed and the adrenaline and noradrenaline selectively adsorbed on aluminum hydroxide and filtered. The precipitate was washed and redissolved with 2N sulphuric acid. The remaining salts were precipitated out by mixing the extract with alcohol and acetone. The filtrate was concentrated in vacuo. The method of extract preparation and bioassay has been described in detail elsewhere.[7-9]

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3. Biologic assay. The blood pressure of the cat was used in conjunction with the rectal cecum of the hen.

A. BLOOD PRESSURE OF CAT. The blood pressure of the cat was recorded from the carotid artery, and injections of adrenaline, noradrenaline, and urinary extract were made into the femoral vein.

B. RECTAL CECUM OF HEN. Two to three centimeters of the rectal cecum of the hen was suspended in Tyrode's solution at 39°C. Injections of adrenaline, noradrenaline, and urinary extract were made into the bath, and the degree of cecal relaxation was recorded.

C. COMPUTATION OF RESULTS. After determination of the activity ratio for adrenaline and noradrenaline on the blood pressure of the cat and the rectal cecum of the hen, and the activity of the unknown urinary extract in terms of l-noradrenaline, it is possible to calculate the relative amounts of adrenaline and noradrenaline in the urinary extract.

4. Fluorometric assay. The fluorometric method of von Euler and Floding[10] was used to screen all patients. This method depends upon the differential oxidation rate of adrenaline and noradrenaline at pH 6.0 and pH 3.5. At pH 6.0, both catecholamines are oxidized within a period of 2 minutes, whereas at pH 3.5, the adrenaline in the presence of zinc sulfate is completely oxidized within 3 minutes, but only 5 per cent of the noradrenaline is oxidized. Urine from those patients who showed fluorometrically an elevated output of adrenaline and/or noradrenaline was also bioassayed for adrenaline and noradrenaline. A Farrand Model A fluorometer was used to measure fluorescence.

Results

The normal 24-hour output varies from 10 to 30 μg for adrenaline and from 20 to 60 μg for noradrenaline. Calculated on the basis of a 24-hour output, the average quantity of adrenaline and noradrenaline excreted by normotensive adult males was 15.7 and 32.3 μg, respectively. These normal results compared well with those of von Euler.[7]

Of the 500 hypertensive patients followed, 73.9 per cent showed a normal output of noradrenaline. However, 10.8 per cent were shown to have a urinary output of noradrenaline in excess of 90 μg per 24 hours, 5.5 per cent in excess of 120 μg per 24 hours, and 3.0 per cent in excess of 180 μg per 24 hours (see Table I). Of the patients who had an output of noradrenaline in excess of 180 μg per 24 hours, 76.6 per cent were proved surgically to have a pheochromocytoma; since the urinary noradrenaline was persistently greatly elevated (300 to 3,190 μg per 24 hours) in the patients with pheochromocytoma, there was no difficulty in delineating this group of patients from the other hypertensive subjects with an elevated output of noradrenaline.

The two specifically selected cases are summarized in the following paragraphs.

Case 1

Clinical summary. E. E., a 40-year-old white highway patrol dispatcher, entered the hospital on March 27, 1956, with the chief complaint of blurring of vision. He had considered himself to be in good health until 15 years previously (age 25), when he was found to have elevated blood pressure (exact levels not known). In the following year, he developed early morning occipital headaches, which became increasingly more severe. On follow-up examinations, he was found to have blood pressure levels of 150/100 to 180/110 mm. Hg. Two years prior to admission, he noted dyspnea on exertion, easy fatigability, syncopal attacks related to exercise, and increased emotional irritability. Four days prior to admission, he noted blurring of vision.

Family history. The patient's father died at age 50 of "stroke" following long-standing arterial hypertension; the paternal aunt had also died of hypertension.

The patient was the oldest of 3 children of a couple in the lower middle-income group. He related that his father had been a firm, restrictive individual and that he had not felt close to him. He was always his mother's "favorite." He emphasized that he never felt quite "sure" of himself and always depended upon his mother for help and direction. He characterized himself as an individual who did not express his feelings easily, particularly those of hostility.

He married at the age of 23 years but maintained close ties with his mother; his mother lived nearby, and each day he visited her. He reported that his wife and mother were antagonistic to each other, and although he often felt his wife's position to be correct, he could not bring himself to the point of contradicting or openly differing with his mother. He recognized that the increasing feelings of "nervousness" and "irritability" were directly related to these relationships involving his wife and mother, and this, in turn, led to feelings of doubt and anger—"I feel all bottled up . . . tight . . . blue."

On physical examination, the blood pressure,

Table I. *Distribution of noradrenaline excretion in 500 cases of idiopathic hypertension (all figures are in μg per 24 hours)*

	Urinary noradrenaline (in μg per 24 hours)						
	<30.0	*30.0 to 60.0*	*60.0 to 90.0*	*90.0 to 120.0*	*120.0 to 140.0*	*140.0 to 180.0*	*180.0*
Per cent distribution	36.5	37.4	15.0	5.3	1.0	1.5	3.0
	Total normal output is 73.9%		Fringe group 15.0%	Total hypersecretion is 10.8%			

with the patient lying and sitting, was 260/170 mm. Hg; the pulse was 120 per minute. Positive findings included the following: Funduscopic examination revealed bilateral papilledema, extensive hemorrhages and exudates, arteriolar narrowing with areas of focal constriction, and fullness of the veins. The heart was not enlarged. The aortic second sound was loud and snapping. The mitral first sound was accentuated. Neurological examination revealed a decrease in visual acuity, but the findings were otherwise unremarkable.

Accessory clinical findings. Hemoglobin was 14.6 Gm. per cent; white blood cell count, 12,500/mm.^{3}; differential normal. Urinalysis: pH 5.5, specific gravity 1.010; traces of protein; 1-2 white cells, no casts on microscopic examination. Fishberg concentration test: specific gravity 1.016; phenolsulfonphthalein excretion, 65 per cent in 2 hours.

The nonprotein nitrogen was 34 mg. per cent; cholesterol, 320 mg. per cent; fasting blood sugar, 129 mg. per cent; protein-bound iodine, 9.8 mg. per cent; basal metabolic rate, −9 per cent; I^{131} uptake, 35 per cent; sodium, 143 mEq./L.; potassium, 3.5 mEq./L.; CO_2, 33 mEq./L.; chloride, 100 mEq./L.; glucose tolerance test: fasting 111, 1 hr., 287, 2 hr., 204, 3 hr., 80 mg. per cent. Electrocardiogram: left ventricular ischemic pattern. X-ray films: skull and chest, normal. Intravenous pyelogram: right bifed renal pelvis and ureter without stones or distortion.

Regitine test and Amytal test: both resulted in modest falls in blood pressure, but neither exceeded 40 mm. Hg systolic pressure or 20 mm. Hg diastolic pressure. These drops were transient in both instances.

The patient was begun on a dietary regimen of rice and fruit and treated with Ansolysen, reserpine, and Apresoline. Furthermore, efforts were directed toward readjusting his domestic life. Gradually during the next 6 weeks, the blood pressure fell to 160/100 and 150/80 mm. Hg. The papilledema receded by the fifth week, and almost all hemorrhages and exudates had resolved by the twelfth week. His activity was gradually increased, and after 3½ months of hospitalization he was discharged.

He returned to work but noted the development of weakness and easy fatigability. Readings of blood pressure taken at home gradually increased in spite of conscientious use of medication and restriction of the intake of salt. He was then readmitted to the hospital on Nov. 19, 1956, for re-evaluation.

Physical examination at this time demonstrated a blood pressure of 160/110 and 230/130 mm. Hg, with the patient standing and lying, respectively. The pulse rate was 104. There was some increase in the light reflex to the arterioles of the fundi, and the aortic second sound was accentuated.

Accessory clinical findings. Maximum concentration of urine was 1.018; phenolsulfonphthalein, 65 per cent in 2 hours; I^{131} uptake, 21 per cent in 24 hours; oral glucose tolerance decreased. Regitine test was negative; 24-hour excretion of 17-keto steroids was 20.0 mg.

The course in the hospital was primarily concerned with the regulation of his drug therapy and counseling for the depressive reaction. After 2 months, his blood pressure was maintained at 120/80 mm. Hg. He was discharged and has returned to work, continuing his program of restricted intake of salt and antihypertensive medication.

Catecholamine summary. On admission, two 24-hour samples of urine were collected and bioassayed for adrenaline and noradrenaline. This was repeated during hospitalization, at the time of discharge, and 1 year later. The results of these findings show that the sympathetic nervous activity, as represented by the urinary noradrenaline, was markedly elevated on admission, i.e., 182.0 μg per 24 hours, but during the course of treatment this gradually decreased, so that by the time of discharge it was almost within normal limits. Two years subsequent to discharge, the noradrenaline had declined to 15.8 μg per 24 hours, or, that is, it was within normal limits. There was a commensurate decline in the blood pressure (see Table II). The urinary adrenaline, on the other hand, varied from specimen to specimen, and, in general, was slightly elevated.

Case 2

Clinical summary. N. S., a 34-year-old white married woman, was first found to have an elevated blood pressure 2 years prior to admission, during the last trimester of her second pregnancy. She had always considered herself to be in excellent health until that time. She was placed on reserpine, and, although increasingly larger doses were required,

the blood pressure was controlled at normotensive levels. The delivery was uncomplicated. During the postpartum period, the blood pressure remained elevated whenever withdrawal of medication was attempted. Frontal headaches developed and were occasionally relieved by aspirin. The headaches were nonpulsatile in type and at times were apparently related to specific life situational stresses.

In the 6 months prior to the initial hospitalization she had discontinued all medication, but noted increasing feelings of depression, and had begun to use alcoholic beverages frequently.

There was a family history of hypertensive vascular disease. The father died at age 44 of cardiac failure secondary to hypertension; a younger sister died 1 year previously of a subarachnoid hemorrhage, having had recognized hypertension for 5 years.

The recent personal history was marked by periods of intense conflict and unrest. The patient was the oldest of 2 children born to a couple in the upper-income group. She considered her family a tightly knit, comfortable group. She felt closest to her father and experienced a period af deep depression at the time of his death. Shortly after her father's death, her sister died, and the patient became quite morose. Her excessive intake of alcohol began at this time.

In the months preceding the first admission she had experienced increasing conflict with her husband concerning his relationship to her and the two children.

On physical examination, the blood pressure was 160/90 mm. Hg; the pulse was 72. She appeared fatigued and anxious. Funduscopic examination: clear. The lungs were clear. The heart was normal in size. The aortic second sound was accentuated. There were no murmurs.

Accessory clinical findings. Hemoglobin was 11.6 Gm. per cent; white blood cell count, 6,200/mm.^{3}; normal differential. Urinalysis: specific gravity 1.012; traces of protein; clear on microscopic examination. Regitine test was normal. Phenolsulfonphthalein excretion total was 70 per cent in 2 hours. Nonprotein nitrogen was 26 mg. per cent; fasting blood sugar, 110 mg. per cent; cholesterol, 175 mg. per cent. Electrocardiogram was normal. Chest x-ray examination was normal. Intravenous pyelogram was normal.

While in the hospital, the patient was placed on modified bed rest. Gradually, the level of the blood pressure decreased, and after 1 week was 130/70 mm. Hg. During hospitalization she was frequently seen by her attending psychiatrist.

During the ensuing 20 months the level of the blood pressure fluctuated markedly. During this period she received intensive psychotherapy, and there was some modification of her adjustment problems. She received mild sedative therapy in addition. No specific antihypertensive medications were employed.

Catecholamine summary. On admission, the 24-hour urinary noradrenaline was 98.4 μg, and 3 weeks later it was 182.5 μg. The blood pressure on admission was 150/100 mm. Hg. As the patient responded to treatment, this high output of noradrenaline gradually decreased, so that at the time of discharge it was 27.0 μg, that is, well within normal limits. There was a corresponding decline in the blood pressure (see Table II). The output of adrenaline remained, for the most part, within normal limits.

Discussion

Sympathetic nerves carry vasoconstrictor fibers to arteries, arterioles, and arteriovenous anastomoses.[5,6] It is now generally accepted that the neurotransmitter substance of the sympathetic (adrenergic) nerves is noradrenaline,[1,11] and that this hormone is released as such at the sympathetic nerve endings. Furthermore, under increased activity of the sympathetic nerves, such as that resulting from specific emotional[12-14] or physical stresses,[8,15,16] there is an increase in the release of this hormone, and this increase in release is reflected in the urine as an elevation in the urinary output of free and conjugated noradren-

Table II. *Output of noradrenaline and adrenaline in 2 hypertensive subjects who showed clinically an increase in sympathetic nerve activity*

Subject	*Specimen number*	*Date of collection*	*Adrenaline (μg/24 hr.)*	*Noradrenaline (μg/24 hr.)*	*Blood pressure (lying)*
Case 1 (E.E.)	1	March 30, 1956	25.0	182.0	260/170
	2	May 2, 1956	41.0	83.9	140/90
	3 (Discharged)	Oct. 22, 1956	65.7	55.0	160/110
	4	Sept. 20, 1959	21.7	15.8	140/90
Case 2 (N.S.)	1	Feb. 26, 1958	32.6	98.4	150/100
	2	March 11, 1958	21.3	182.5	140/90
	3	March 24, 1958	11.3	136.0	140/90
	4	June 9, 1958	47.5	35.4	140/80
	5	Sept. 11, 1959	18.1	27.0	130/70

aline. It is well established that noradrenaline elevates the blood pressure.[17-19]

Although noradrenaline is also found in the adrenal medulla, the principal hormone of the human adrenal medulla is adrenaline.[20] Both of these hormones are released in increased amounts under various forms of stress, i.e., burns,[8] muscular exercise,[15] centrifugation,[16,21] X-irradiation,[22] etc.

Since adrenaline is a general vasodilator,[17,19] hypertension could not result from any increase in the output of adrenaline. On the other hand, noradrenaline elevates both the systolic and diastolic blood pressure,[17-19] and, therefore, an increase in the activity of the sympathetic nerves, with a concomitant increase in the release of noradrenaline, could produce a hypertensive state. However, it should also be emphasized that a large number of hypertensive subjects with increased vasomotor activity do not show an elevation in the output of noradrenaline; therefore, their hypertension must be the result of something other than an increase in sympathetic nerve activity (see Table I, "normal output").

Although this paper describes in detail only 2 cases of idiopathic or essential hypertension, it demonstrates that, at least in these 2 cases, the hypertension seems to result from an increased sympathetic nerve activity as manifested by an increase in the urinary output of the sympathetic neurohormone, noradrenaline. Furthermore, it would appear that this increase in sympathetic nerve activity, in turn, was related in these particular patients to an increase in activity of such higher nerve centers as the cortex, since both of these patients were greatly disturbed over their personal and domestic problems. Therefore, one would seem justified in concluding that possibly other such similar hypertensive cases exist and that these should be searched for and studied in detail.

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Effect of variations in cardiac output and diastolic filling period upon the mitral diastolic gradient

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The magnitude of the mitral diastolic gradient in subjects with mitral stenosis is a function of the size of the mitral valve and the subvalvular area, the cardiac output, and the heart rate,[1,2] especially the diastolic filling period. In patients with atrial fibrillation the diastolic gradient varies from beat to beat with variations in the diastolic filling period.[2,3] A progressive fall in the magnitude of the gradient is observed during the latter portion of a long diastolic interval. Conversely, the mean magnitude of the diastolic gradient is elevated during a short diastolic filling interval.

Since both the heart rate and cardiac output may be increased during exercise, it is often difficult to differentiate between the effects of these two parameters upon the mitral diastolic gradient under exercise conditions. In patients with sinus rhythm the variations in the diastolic interval are limited at rest and during exercise. In contrast, in patients with atrial fibrillation, marked variations in the diastolic filling period are usually readily observed both at rest and during exercise. The purpose of this report is to illustrate and differentiate between the effects of variations in diastolic filling period and in flow upon the mitral gradient in 8 subjects with mitral stenosis and atrial fibrillation who were studied by combined right and left heart catheterization. Significant mitral insufficiency was not observed in any of these patients at mitral commissurotomy. Comparable observations have not been previously reported.

Methods and materials

The techniques formerly employed in combined right and left heart catheterization in this laboratory have been described.*[1,2] Cardiac output was determined by the Fick principle, both at rest and during steady-state exercise. The magnitude of the mean diastolic left atrial–left ventricular gradient was determined by planimetry at a paper speed of 75 mm. per second. The diastolic interval was

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*Transseptal left atrial puncture and transventricular left ventricular puncture are now utilized for left heart catheterization.

measured as the duration of the gradient. The latter was measured as the interval during which left ventricular pressure was equal to or less than left atrial pressure. Since the left atrial and ventricular pressure curves were recorded from the same base line and with equisensitive pressure gauges, the determination of the exact crossover points of the atrial and ventricular curves was readily accomplished. The error in measurement of the diastolic period is estimated to be 0.02 or 0.03 second at most. A beat-by-beat analysis was made of all gradients, both at rest and during exercise, and the gradients were plotted against the diastolic intervals.

Results

The relationships between the mitral diastolic gradient and the diastolic interval of that gradient are illustrated in Figs. 1-8 for the 8 subjects studied. The *X* points refer to the exercise data, and the black dots to the data obtained at rest. The decrement in the magnitude of the gradient with increasing diastolic intervals is readily noted, as is the separation between the exercise and rest data. In 7 subjects the exercise gradient is significantly greater than the rest gradient at the same diastolic interval ($p < 0.001$). In one subject (E. Coo.), no significant difference ($0.2 > p > 0.1$) was noted between the data obtained at rest and those during exercise. The clinical and catheterization data for these 8 subjects have been published previously.[2]

The exercise output increments per

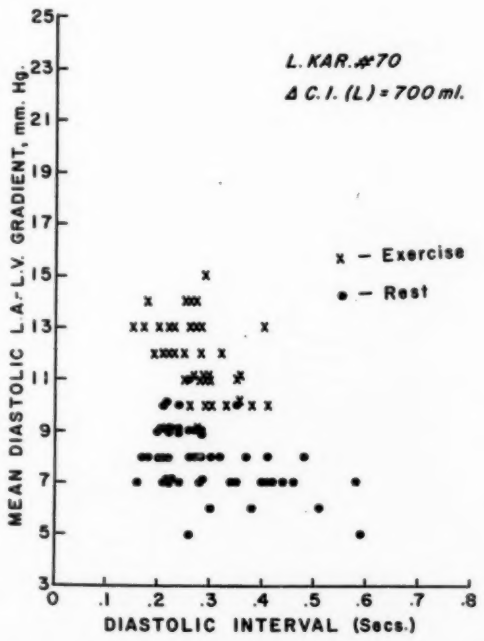

Fig. *1.* Relationship between the mitral diastolic gradient and the diastolic filling interval at rest and during exercise in Subject L. Kar. The increment in cardiac index during exercise is also listed. The exercise gradients are significantly different from the resting gradients at the same diastolic intervals. Oxygen consumption per minute per square meter of body surface area increased from 119 ml. at rest to 196 ml. during exercise.

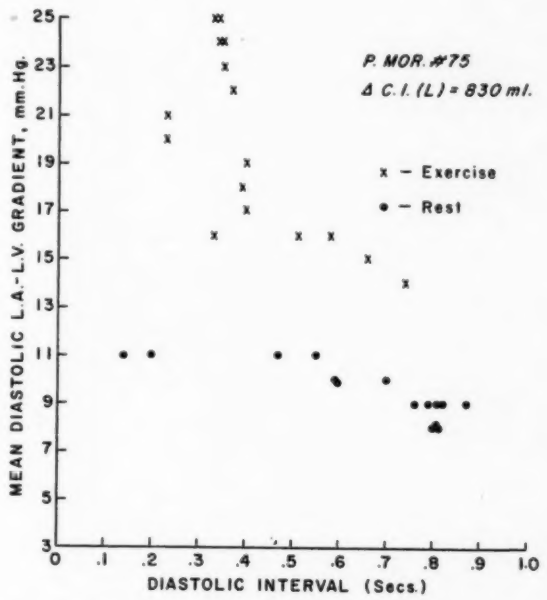

Fig. *2.* Data for P. Mor. Oxygen consumption during exercise rose from 111 to 226 ml./min./M.^{2}.

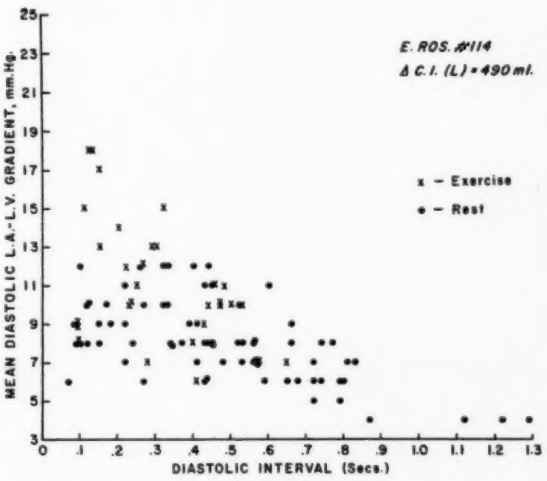

Fig. *3.* Data for E. Ros. Oxygen consumption during exercise increased from 104 to 213 ml./min./M.^{2}.

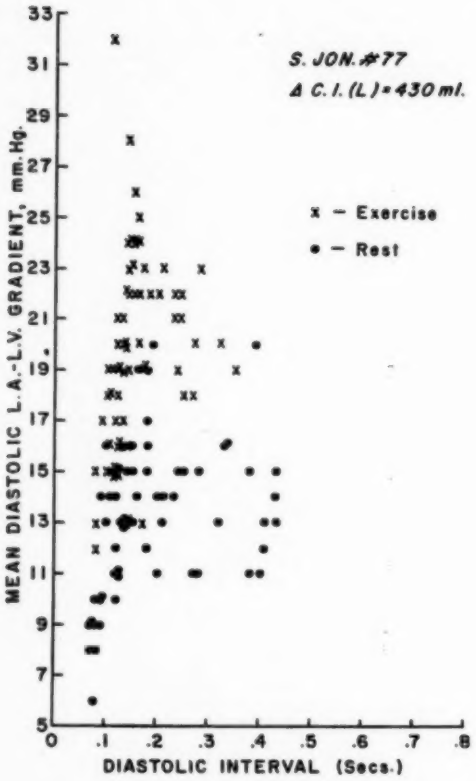

Fig. 4. Data for S. Jon. Oxygen consumption rose from 138 to 227 ml./min./M.².

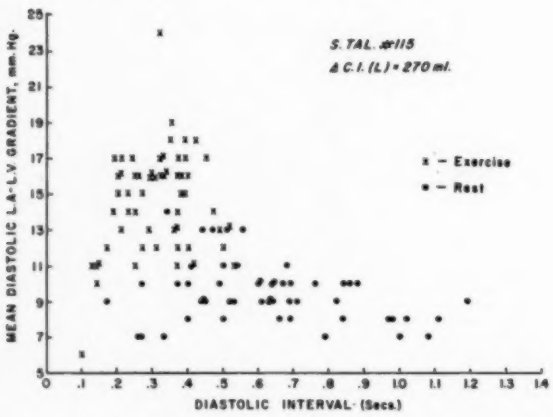

Fig. 5. Data for S. Tal. Oxygen consumption increased from 102 to 174 ml./min./M.².

square meter of body surface area are shown on the graphs. *L* refers to output data obtained during combined right and left heart catheterization, and *R* to the data determined in the course of the right heart catheterization, which was performed immediately prior to the left heart catheterization. The clear separation between the resting and exercise gradients in the first 7 subjects is not proportional to the level of increment in cardiac output during exercise. Oxygen consumption during rest was approximately doubled during exercise in these 8 patients.

Discussion

Hemodynamic measurements during exercise are frequently performed during right heart catheterization in subjects with mitral valvular disease. Increments in pulmonary arterial pressure under such circumstances may be due to alterations in such parameters as cardiac output, heart rate, pulmonary blood volume, left atrial mean pressure, left ventricular end-diastolic pressure, intrathoracic and pleural pressure, and pulmonary arterial vasomotion. Determination of the mean diastolic left atrial–left ventricular gradient during rest and exercise studies affords a more direct method of evaluating the status of the mitral valve. Increments in cardiac output and heart rate may both increase the magnitude of the mitral gradient. If the increase in heart rate is the primary factor in the increase in gradient during exercise, intravenous atropine might theoretically be employed to simulate exercise hemodynamics. If the effects of increments in flow

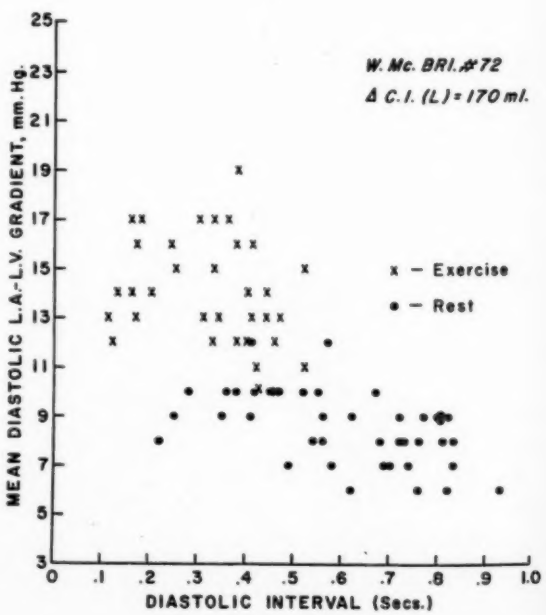

Fig. 6. Data for W. McBri. Despite the minimal rise in cardiac output during exercise, there is a significant difference between the gradients at rest and during exercise. Oxygen consumption increased from 115 to 224 ml./min./M.².

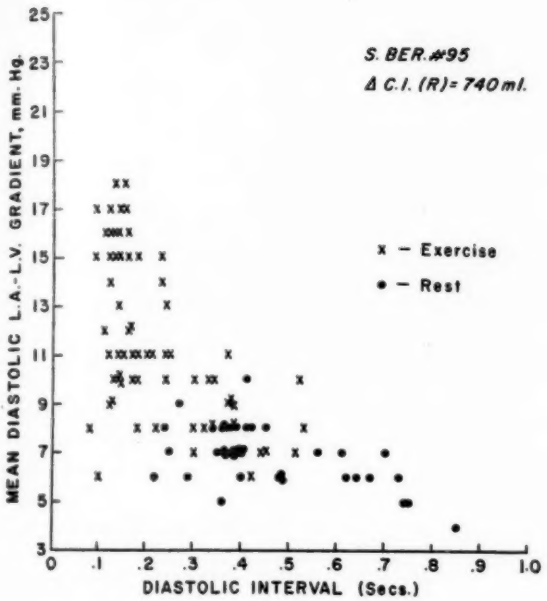

Fig. 7. Data for S. Ber. Exercise output data were obtained during right heart catheterization. Oxygen consumption rose from 100 to 222 ml./min./M.².

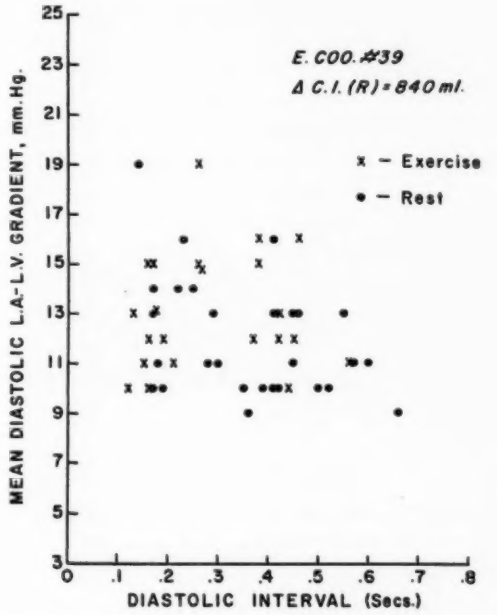

Fig. 8. Data for E. Coo. There is no significant difference between the gradients obtained at rest and during exercise. The increment in oxygen consumption is from 115 to 228 ml./min./M.².

can be separated from those of rate per se, intravenous administration of atropine (unless accompanied by an increase in cardiac output) could not be utilized to simulate exercise conditions. The data obtained in the 8 patients in this study demonstrate that, in most patients, even small increments in flow result in separation of the resting and exercise gradients at the same diastolic time intervals.

The magnitude of the mitral valvular gradient in any one patient with mitral stenosis is a function of the size of the valve, amount of flow through the mitral valve (or cardiac output in the absence of mitral insufficiency), and the diastolic filling period. Since the latter period shortens proportionately more than total cycle length as the heart rate is increased, the magnitude of the gradient rises during tachycardia per se. The separation between the exercise and rest gradients noted in this study at the same diastolic filling intervals demonstrates that the flow increment during exercise also contributes to the gradient increment observed during exercise.

Summary

The differential effects of alterations in the diastolic filling period of the left ventricle and in cardiac flow upon the mean diastolic left atrial–left ventricular gradient have been investigated in 8 subjects with atrial fibrillation studied at diastolic filling intervals of similar magnitude. The results demonstrate the sensitivity of the magnitude of the gradient to even small alterations in blood flow.

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Experimental and laboratory reports

Analysis of time and concentration components and cardiac output determination obtained from precordial isotope-dilution curves

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Analysis of precordial isotope-dilution curves has proved to be a useful technique for serial determinations of cardiac output.[1-4] Although previous studies[5-14] have outlined the basic technique, necessary calculations, and the close agreement with determinations of output by conventional methods, little information has been accumulated other than that presented by Shackman[15] on the repeatability of these measurements, such as that available for the Fick method.[17] Perhaps because of the variability in instrumentation, few systematic analyses of the time components of the resultant curves, such as those presented by Cornell and associates,[18] have been made. Such an approach has increased the screening value of arterial dye-dilution curves in various disease states, and might be applicable to precordial curves when obtained by a standard technique.

Doses of radioactive iodinated human serum albumin (RIHSA) necessary to obtain satisfactory results have been substantially reduced over those usually reported, probably because of increasing sensitivity of detection equipment. Thus, analysis of curve contours could be widely applied in screening clinics as well as diagnostic laboratories if it were possible to establish the range of variability present in groups of normal subjects.

The purpose of this report is to present further data comparing precordial isotope-dilution cardiac output values with those obtained by the Fick method, to report on the repeatability of this measurement, and to attempt to quantify the contour characteristics of normal curves.

Materials and methods

Ninety precordial isotope-dilution curves (determinations of cardiac output) in 42 patients with no evidence of cardiac disease (34 males and 8 females) have been analyzed. Thirty-four studies were obtained in 15 patients who had cardiac outputs determined according to the Fick principle by means of right heart catheterization. The latter studies were consecutive rather than simultaneous. All patients were in the supine position during the procedure.

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The opinions or assertions contained herein are those of the authors and are not to be construed as official or reflecting the views of the Department of the Navy or the naval service at large.
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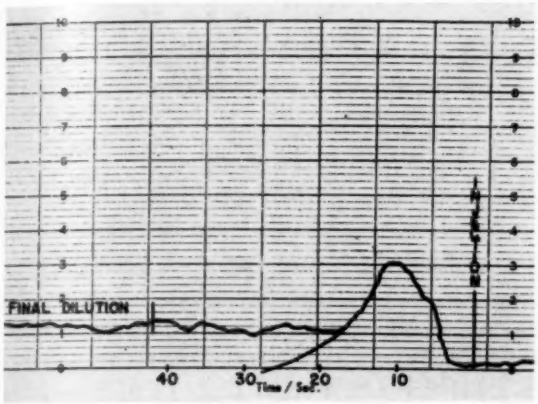

Fig. *1.* Probe focused over apex of heart, fifth left intercostal space in the mid-clavicular line. Cardiac index: 4.33 L./min./M.^{2}.

The method of right heart catheterization in this laboratory has been described elsewhere.[2]

Externally monitored isotope-dilution curves were obtained by positioning a collimated scintillation detector in direct contact with the skin over the second left intercostal space or apex. The detector employed in the probe was a 2.5 by 2.5 cm. thallium-activated sodium iodide crystal shielded with a 2.5-cm. thick straight-bore lead collimator with a diameter of 2.5 cm. and a depth of 3.8 cm. beyond the crystal.

The scintillation probe was connected to a Nuclear-Chicago rate meter with a variable time constant which was set at 2.0 seconds.[19] Dose was dependent on the selection of count rate, which ranged between 3,000 and 30,000 counts per minute. Curves were recorded on a direct-writing linear recorder with a paper speed of 6 inches per minute.

The RIHSA was delivered through a three-way stopcock attached to an indwelling No. 20 Riley needle placed in an antecubital vein. Rapid injection of the RIHSA, contained in a volume of 1 ml., was followed by a 10-ml. flush of normal saline solution. Injection time was marked on the base line, and recording was continued through the primary phase and recirculation. Ten minutes after injection, with the apparatus remaining in place, a final concentration (Ceq) was recorded over a 1-minute period. Radioactivity per study ranged from 5 to 45 microcuries (μc).

In some subjects the blood volume was determined by the RIHSA method.[20] A single-channel gamma-ray spectrometer and scintillation well counter were employed for the counting of blood samples and standard, which were 3 ml. in volume. In the others the blood volumes were estimated from normal standards.[21]

The curves were extrapolated to the base line by plotting points from the descending limb on semilogarithmic paper and then replotting the extrapolation on the initial linear tracing (Figs. 1 and 2). The area under the curve was determined by a compensating planimeter, and cardiac output was calculated according to the formula,

$$F = \frac{Ceq \times B.V.}{Cavg \times T.}$$

F represents flow, Ceq is the final concentration, Cavg is the average concentration during time T, and T is the time of primary passage of indicator through the heart.[5-8]

The time components of the curves were

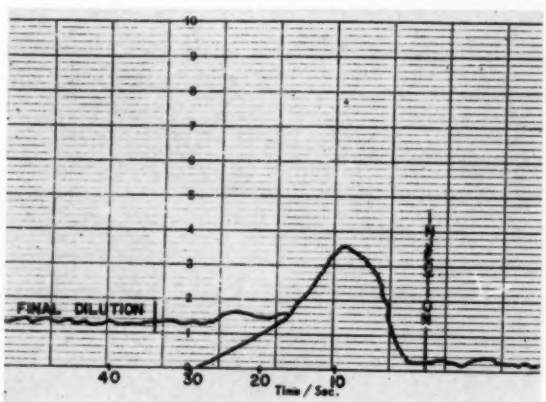

Fig. *2.* Probe focused over second left intercostal space adjacent to sternum. Cardiac index: 4.45 L./min./M.^{2}.

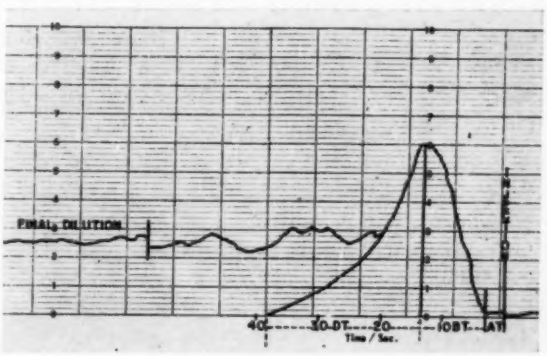

Fig. *3.* Probe focused over second left intercostal space adjacent to the sternum. Appearance time (*AT*); build-up time (*BT*); disappearance time (*DT*). Cardiac index: 3.40 L./min./M.^{2}.

Table I

Ratio	*Normal (41 curves)*		*Shunts (38 curves)*		*p value*
	Mean	*S.D.*	*Mean*	*S.D.*	
$\frac{Cp+BT}{Cp}$	0.54	±0.18	0.71	±0.13	<.001
$\frac{Cp+2BT}{Cp}$	0.32	±0.18	0.57	±0.19	<.001

analyzed according to methods widely applied to arterial dye-dilution curves.[22-24] Appearance time (A.T.) is the number of seconds from the instant of injection to the onset of the upstroke. Build-up time (B.T.) is the number of seconds from the onset of upstroke to the peak of the curve. Disappearance time (D.T.) is the time from the peak to the return of the extrapolated disappearance slope to the base line (Fig. 3). The D.T. divided by the B.T. constitutes the D.T./B.T. ratio and should correct for generalized slowing of time components as occurs with reduced cardiac output or increased volume.[24,25] A number of curves were analyzed for the disappearance ratios $\frac{Cp+BT}{Cp}$ and $\frac{Cp+2BT}{Cp}$ described by Carter and associates.[22] In addition, the ratio obtained by dividing the height at the peak in centimeters (Cp) by the height of the recirculation level (C_R) in centimeters (Cp/C_R ratio) was employed. When an identifiable recirculation peak was not present, the C_R height was taken 25 seconds after injection (the mean time for C_R of the normal subjects).

The standard deviation, correlation coefficient, standard error of a single observation, and standard t test were applied according to the methods of Hill[27] and Mainland.[28]

Results

Analysis of curve contours. Ninety studies from 42 normal subjects resulted in appearance times of 1-15 seconds, rapid upstroke, and an exponential fall-off followed by recirculation and a final concentration level. Generally, curves recorded over the apex were somewhat more spread out than those from the second left intercostal space, having longer build-up (B.T.) and disappearance (D.T.) times but essentially similar D.T./B.T. ratios.

Mean B.T. was 9.9 ± 2.9 sec.; D.T. was 34 ± 9.2 sec.; and the D.T./B.T. ratio was 3.9 ± 1.9. Comparable studies on 32 curves from 18 patients with proved left-to-right shunts yielded the following values: B.T. of 8.3 ± 4.4 sec.; D.T. of 61.5 ± 25.4 sec.; D.T./B.T. ratio of 8.2 ± 2.9. Only 3 of 32 curves in this group resulted in D.T./B.T. ratios of less than 5.0, and each of the 3 patients had one or more repeat studies in which the D.T./B.T. ratio was more than 5.0. Whereas the differences in B.T. values were insignificant, the values obtained for the D.T. and D.T./B.T. ratios between the two groups were significantly different ($p < .001$).

Comparison of 38 curves from 18 patients who had proved shunts with those from 57 normal subjects, utilizing the Cp/C_R

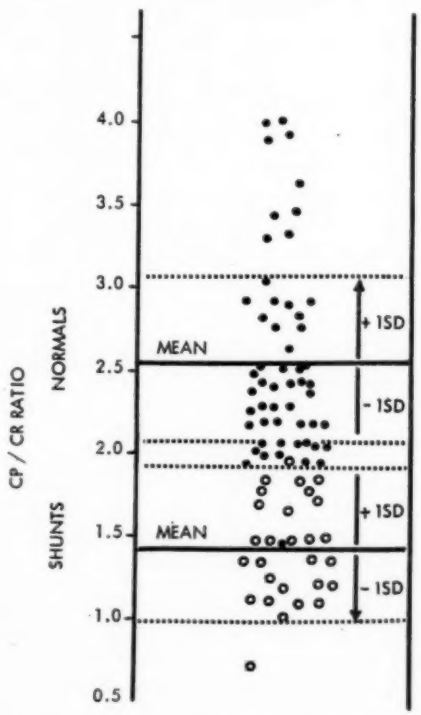

Fig. 4. Comparison of normal and abnormal curves by the Cp/C_R ratio. Each dot represents Cp/C_R ratio of curves obtained in normal subjects, and each circle the Cp/C_R ratio of curves obtained in abnormal subjects. Solid line represents mean, and dotted line the limit of one standard deviation.

Table II

	Number of successive curves	*First group (Mean ± S.D.)*	*Second group (Mean ± S.D.)*	*p value*
D.T./B.T. ratio	40	5.5 ± 3.4	5.5 ± 3.0	>0.9
$\frac{Cp+BT}{Cp}$ ratio	28	.71 ± .14	.71 ± .13	>0.9
Cp/C_R ratio	46	1.91 ± .50	1.89 ± .10	>0.3

ratio, revealed a mean ratio of 2.6 ± 0.55 in the normal and a mean of 1.4 ± 0.59 in the abnormal (Fig. 4). Analysis showed these differences to be significant ($p < .001$).

The results of comparisons utilizing other disappearance ratios are given in Table I, and the repeatability of the various disappearance ratios are shown in Table II.

Comparison of precordial isotope-dilution and Fick outputs. Comparison of isotope data with data obtained by the Fick method in 15 catheterized patients showed good agreement between the two techniques ($r = +0.97$), with deviations of the isotope-dilution measurement from the Fick values ranging from −16 to +10 per cent. Mean deviation was 8.8 per cent (Fig. 5; Table III). Mean cardiac index by the isotope method was 3.44 ± 0.31 L./min./M.².*

Repeatability of precordial isotope-dilution cardiac output determinations. Two successive cardiac outputs were determined in 37 normal subjects, 3 successive studies in 4 subjects, and 4 successive studies in 1 subject (total radioactivity injected into the latter was 93 μc). The mean value for the 42 initial studies was 5.67 L./min. ± 1.84. The mean for the 42 second studies in these same individuals was 5.54 L./min. ± 1.43. The differences were not significant ($p > 0.9$). The standard error of an individual determination of output was 0.51 L./min. Mean cardiac index for the entire series was 3.77 ± 0.30 L./min./M.².

Discussion

The close agreement between the outputs determined by the isotope-dilution method and those obtained according to the Fick principle in this study lends further support to the previous data of others who reported nearly identical results from isotope-dilution, dye-dilution, and Fick techniques.[7,8,10,11,15,16]

The good reproducibility of results from repeated curves obtained in the same individual demonstrate that the slight variations in the recorded curves are of no significance for this determination. The results confirm the relative stability of successive determinations of cardiac output in supine subjects as shown by the Fick method.[17] The values obtained for cardiac index and standard error of a single determination in the normal subjects who did not have Fick determinations compare favorably with those obtained by the Fick method in normal subjects, as reported in the literature.[17]

Precordial isotope-dilution curves provide a convenient means of screening

Table III. *Comparison of Fick and precordial output*

Subject	*Precordial (L./min.)*	*Fick (L./min.)*
1.	3.5	3.5
2.	4.3	4.5
3.	5.9	5.4
4.	9.7	11.3
5.	4.2	4.4
6.	6.6	6.0
7.	3.2	3.4
8.	8.4	8.7
9.	4.2	4.0
10.	6.2	6.3
11.	7.5	8.5
12.	6.2	6.7
13.	5.0	5.7
14.	5.4	6.4
15.	4.9	4.5
Mean	5.68	5.93
S.D.	±1.76	±2.11
$r = +0.97$		

*Three patients were excluded from the study because they moved during inscription of the primary curve or equilibration phase.

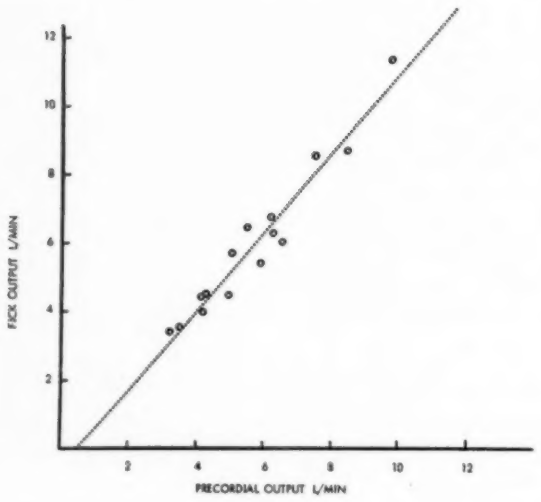

Fig. 5. Comparison of Fick and precordial output on 15 subjects ($r = +0.97$).

patients for certain disease states by comparison of the time component relationships with those obtained from a normal control group. In addition, analysis of successive curves in the same patient for D.T./B.T., Cp/C_R, and disappearance ratios give good reproducibility. Reliable serial determinations of cardiac output may be readily made from those patients who have normal curves.

The derivation of normal values for selected time components of precordial isotope-dilution curves might allow such analyses of the curves to aid in the detection and evaluation of such pathologic conditions as congestive heart failure, left-to-right shunting, and valvular insufficiency, as is the case with conventional dye-dilution techniques. In order to obtain relatively reproducible curves in individual subjects it was necessary to follow a rigid routine of rapid injection with immediate flush while focusing as accurately as possible over the selected sites. One could thus deliver the indicator as a bolus to the central circulation, as well as avoid distortions of the curve that are known to occur when counting is done over the right atrium or great veins.[9,10]

With the technique employed, appearance time was a variable and unreliable component. Its length was probably as closely related to speed of injection and the distance from antecubital fossa to heart as it was to the subject's circulation time. Injection into the femoral vein without flush might provide better values for appearance time. In some patients with heart failure the appearance time has been greatly prolonged, but in a limited series of patients with right-to-left shunts it has not been helpful. Simultaneous detection over the heart and a peripheral artery has been demonstrated to be useful in the detection of right-to-left shunting.[26]

Values for B.T. and D.T. and D.T./B.T. were somewhat greater than those obtained from arterial sampling.[23,24] This may, in part, be explained by the fact that the precordial detector was recording curves that were impure in varying degree rather than a simple outflow curve as obtained by arterial sampling. Nevertheless, analysis of curve contours by means of the D.T./B.T. and Cp/C_R ratios, as well as the disappearance ratios of the Mayo group,[22] appeared to distinguish the group with left-to-right shunts from the normal group. Normal or abnormal ratio values obtained in a given patient, however, require cautious interpretation in the light of the clinical and other laboratory data. It is quite possible that gross valvular insufficiency may produce similar results. Theoretically, the type of analysis utilized should sort out the slow, low curves of heart failure in which normal disappearance ratios would be expected because of the proportionate prolongation of all time components. Comparison of these data with those obtained in other laboratories employing similar methods and equipment should ultimately reveal the value of analysis of curve contours as an aid in the diagnosis of certain lesions.

Summary

1. Comparison of precordially measured cardiac outputs with consecutive Fick determinations revealed good agreement.

2. Repeated cardiac output values obtained by the isotope method agreed closely, and figures for cardiac index were in the normal range for the normal group studied.

3. Analysis of time components and various disappearance ratios of precordial isotope-dilution curves from normal subjects were presented and compared with results of similar analyses carried out in a group of subjects with proved left-to-right

shunts. It appeared possible to distinguish the groups, but individual curves required cautious interpretation.

4. Comparison of time components and disappearance ratios in successive curves on the same subject showed that closely reproducible results were obtained.

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Theoretical and clinical studies of the electrocardiogram and vectorcardiogram in right ventricular enlargement

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One limitation of the electrocardiogram in the recognition of right ventricular enlargement is the difficulty of differentiating manifestations of this lesion from those of right bundle branch block. Evidence that the spatial vectorcardiogram is useful in making this differentiation has been reported, but a theoretical basis for different vectorcardiographic effects has not been established.[1] Without such a basis, the evidence for differential value of the vectorcardiogram has been difficult to evaluate, since there is no certain method of separating patients with enlargement and the conduction disorder from those with only enlargement or only the conduction disorder. One object of the present study was a theoretical investigation of the electrocardiographic and vectorcardiographic effects of right ventricular enlargement and of right bundle branch block. Results of this investigation indicated that these lesions may be expected to produce different vectorcardiographic manifestations, and defined a theoretical basis for these differences.

Another object of this study was a theoretical investigation of the electrocardiographic and vectorcardiographic effects of different varieties of right ventricular enlargement. The effects of generalized hypertrophy, hypertrophy of the free wall, hypertrophy of the inflow and outflow tracts, and the effects of dilatation were contrasted. Results of this portion of the investigation indicated many similarities in the electrocardiographic and vectorcardiographic effects of the various types of enlargement postulated, but also indicated certain differences which seem worthy of clinical and experimental investigation to evaluate their diagnostic value.

A further object of this study was to employ some of the insights provided by the theoretical investigations in the analysis of electrocardiograms and vectorcardiograms of patients with right ventricular enlargement. The theoretical investigation suggested that the quantity described by Burger and Vaane under the term "polar vector" is a promising parameter of right ventricular enlargement, and the clinical portion of the present investigation supported this promise.[2]

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Methods and materials

Theoretical studies. The normal ventricular excitation sequence and that of experimental right bundle branch block as reported by Scher were employed in these studies.[3,4] Spatial vectorcardiograms and standard electrocardiographic leads were derived from these data, by means of a method which has been previously applied to ventricular excitation.[5] The theoretical basis for this analysis was presented in detail in a previous publication reporting a similar analysis applied to atrial excitation.[6] In this method, excitation wave fronts at each of several moments on four horizontal and four frontal plane diagrams of the vertically oriented heart were considered. When a wave front was interrupted by the external or internal surface of the heart, the interrupted ends of the front were joined by a line, and a vector was constructed perpendicular to the line and given a magnitude proportional to the length of the line multiplied by a factor proportional to the thickness of the slice from which it was derived. Vectors derived from simultaneous fronts on all horizontal plane diagrams were added and their projections on horizontal (X) and anteroposterior (Z) axes were determined. Similar addition of vectors from frontal plane diagrams was carried out and projection of final vectors on a vertical (Y) axis was determined. The values of vectors projected on X, Y, and Z axes were then employed to diagram frontal and horizontal plane projections of the QRS loop, and three-dimensional wire models were constructed from these projections. The models were oriented to approximate the anatomic position of the human heart, and frontal, left sagittal, and horizontal plane views of the models in this new position were obtained by tracing their projections on each of these planes. Standard electrocardiographic leads were derived from the projections of frontal plane loops on the sides of an equilateral triangle. Detailed deviation of precordial leads from the vectorcardiograms was not attempted, but vectorcardiographic features which would be likely to result in an R′ pattern in Leads V_1 or V_2 were noted when they occurred.

Records derived from the normal excitation sequence were considered to be controls. Other records were derived from the excitation sequence reported by Scher in experimental right bundle branch block and after postulation of various degrees and types of right ventricular enlargement. The types of enlargement postulated were dilatation, hypertrophy of the free wall and septum, and hypertrophy localized to the free wall and to the approximate regions of the inflow and outflow tracts. Increases in linear dimensions of 25, 50, and 100 per cent were employed for each of these situations. With postulated dilatation the normal thickness of the right ventricular wall was retained. With hypertrophy involving the septum the right one third of the septum was arbitrarily considered to be part of the right ventricle. Direct detailed demonstration of the excitation sequence in the presence of right ventricular enlargement has not been carried out, so that for the purposes of the present study this sequence was approximated, with the normal activation pattern used as a guide. In the case of hypertrophy the excitation fronts representing the normal activation pattern were extended into the thickened portions of the ventricular wall. With dilatation it was assumed that conduction velocity was the same as in the normal heart, and that the mode of delivery of excitation to the endocardial surface was similar to that in the normal heart but extended over a greater area. Although there is no direct evidence that the excitation pattern postulated is the correct one, the derived records had the features known to be associated with right ventricular enlargement in clinical electrocardiography.

Clinical studies. Fifty normal subjects and 34 patients with right ventricular enlargement were studied. A medical history, physical examination, roentgenogram and/or fluoroscopy of the chest, and conventional 12-lead electrocardiogram were obtained in each case. All of the patients who were classified as having right ventricular enlargement had heart disease of a type which was expected to result in enlargement of the right ventricle, and all had roentgenographic evidence of such enlargement. Eight had rheumatic heart disease with mitral stenosis, 16 had congenital heart disease, 3 had primary pulmonary

hypertension, and 7 had cor pulmonale secondary to emphysema. The electrocardiograms of 15 patients fulfilled Milnor's criteria for right ventricular enlargement.[7] The electrocardiograms of the other 19 patients showed nonspecific abnormalities. These findings do not reflect the adequacy of Milnor's criteria for right ventricular enlargement, since a specific search was made for patients with roentgenographic evidence of enlargement but without definite electrocardiographic evidence of this lesion.

Frontal, left sagittal, and horizontal plane projections of the spatial vectorcardiogram were obtained on all subjects by means of the Frank precordial lead system. The gross features of direction of inscription, general contour, and orientation of the QRS loop in each of these planes were noted. In addition, the "polar vector" was determined. For this determination the areas of frontal, sagittal, and horizontal plane projections of the QRS loop were measured with a planimeter. For each of these QRS areas a vector was defined with a length proportional to the area, a direction perpendicular to the plane of the area, and sense such that it pointed away from the side of the QRS-loop projection in which the direction of inscription was counterclockwise. These vectors were added to give the "polar vector," which was described in terms of its magnitude and the angles ψ and ϕ, representing, respectively, the angle between the "polar vector" and the vertical axis and the angle between the Z axis and the projection of the "polar vector" on the horizontal plane. The special merit of this quantity in the recognition of right ventricular enlargement was suggested by the theoretical studies and will be considered further under the sections on results and discussion.

Results

Theoretical studies. Records derived after postulated right ventricular enlargement and from the excitation sequence of right bundle branch block had general characteristics known to be associated with these lesions from clinical electrocardiographic and vectorcardiographic experience. These will not be described in detail, but, as examples, right ventricular enlargement shifted the frontal plane projection of the QRS loop and the electrical axis of the ECG toward the right. Right bundle branch block yielded a QRS loop with the terminal portion located to the right of the isoelectric point, resulting in a wide, deep S wave in the derived Lead I. In addition to the commonly accepted ECG and VCG manifestations of right ventricular enlargement the derived curves showed several effects which are less well known as manifestations of this lesion, and these will be described in greater detail.

Several ECG and VCG effects were common to all varieties of right ventricular enlargement postulated, so that the results will not be described individually for each type of enlargement. The direction of inscription and the area of the horizontal plane projection of the QRS loop seemed to be promising indices of right ventricular enlargement, and some of the results will be presented under this heading. Other results were pertinent to an explanation of the occurrence of R′ patterns in Leads V_1 and V_2 and will be presented under that heading. Still other results indicated that posterior displacement of the QRS loop may sometimes be the result of right ventricular enlargement and will be described under that heading. Finally, the effects of right bundle branch block on the derived electrocardiograms and vectorcardiograms will be contrasted with the effects of enlargement. Examples of records derived from the normal excitation sequence and that of right bundle branch block and from several postulated varieties of right ventricular enlargement are shown in Fig. 1; references to this figure will be made in the following sections.

DIRECTION OF INSCRIPTION AND THE AREA OF THE HORIZONTAL PLANE PROJECTION OF THE QRS LOOP. The normal counterclockwise inscription of the QRS loop in the horizontal plane has been reported to be altered in right ventricular enlargement and to be unchanged in right bundle branch block.[1] The present study confirmed the likelihood of this alteration, and provided insight into its mechanism as well as its limitations as an index of right ventricular enlargement.

The direction of inscription of a plane projection of the QRS loop depends on the

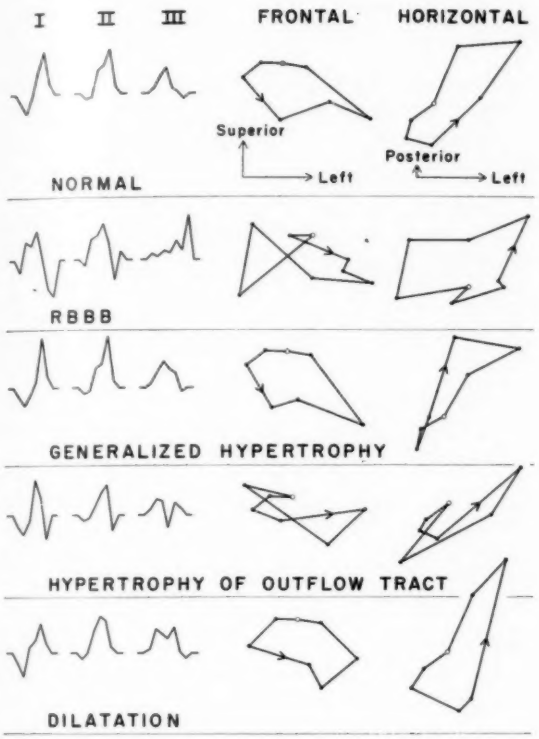

Fig. *1*. Electrocardiograms and vectorcardiograms derived as described in the text from the normal excitation sequence, that of right bundle branch block, and after postulated generalized hypertrophy, hypertrophy of the outflow tract, and dilatation. In each instance the effect of 50 per cent increase in linear dimensions is illustrated. Note that the horizontal projection of the normal QRS loop and those of right bundle branch block and of dilatation are inscribed in a counterclockwise direction, whereas those of generalized hypertrophy and hypertrophy of the outflow tract are inscribed in a clockwise direction. Also note that localized hypertrophy of the outflow tract results in greater rightward displacement of late vectors than does generalized hypertrophy and would be more likely to be associated with an R′ pattern in Lead V_1 and/or Lead V_2. As shown in the horizontal projection, dilatation results in greater anterior extension of the first half of the QRS loop than do the other postulated abnormalities.

relative positions of efferent and afferent limbs. The basic reason that right ventricular enlargement altered the direction of inscription in some of the derived records was that the position of the terminal portion of the afferent limb in the horizontal plane was not so markedly altered by the postulated lesion as was the position of mid-temporal portions of the loop. In turn, the reason for less alteration of the terminal portion of the afferent limb was the relative thickness of right and left ventricular walls. As long as the normal left ventricular wall remained thicker than the hypertrophied right ventricular wall, activation in the left ventricle was still the major determinant of the position of the terminal portion of the afferent limb in the horizontal plane. The initial portion of the efferent limb also remained fixed with postulated right ventricular hypertrophy, since the normal excitation pattern was employed in the inner portions of ventricular walls. The later portions of the efferent limb and early portions of the afferent limb, which will be designated as the "mid-temporal" portion of the QRS loop, were altered by right ventricular enlargement. As illustrated in Fig. 2, these portions of the loop were displaced toward the right by right ventricular hypertrophy, and this displacement, together with a relatively fixed terminal portion of the loop, sometimes produced clockwise rotation of the QRS loop in the horizontal plane. Increasing degrees of right ventricular hypertrophy had increasing degrees of influence on the orientation of vectors in the mid-temporal portions of the loop. With the initial and terminal portions of the loop relatively fixed, this resulted in either a smaller area of the horizontal plane loop, or actual reversal of its direction of inscription. The foregoing description applied to all varieties of right ventricular hypertrophy postulated. Records derived after postulated hypertrophy of the outflow tract and generalized hypertrophy are shown in Fig. 1, and in both instances the major area in the horizontal plane is inscribed in a clockwise direction.

Right ventricular dilatation had a more complex effect. Dilatation resulted in anterior displacement of early portions of the efferent limb. The basis of this effect is illustrated diagrammatically in *A* and *B* of Fig. 3. This displacement complicated the effects of right ventricular enlargement on QRS area in the horizontal plane, since, acting alone, it would have produced an increase in area. Thus, dilatation combined with ventricular hypertrophy had less effect on the total area of the QRS loop in the horizontal plane than did the same degree of hypertrophy acting alone. As shown in Fig. 1, postulated dilatation with 50 per cent increase in the linear dimensions of the right ventricular cavity resulted

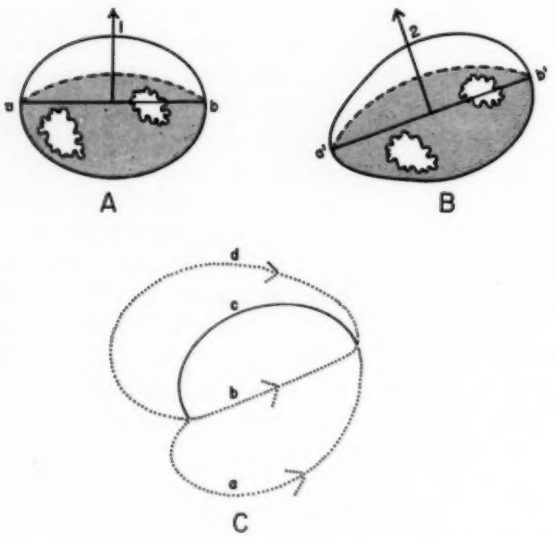

Fig. 2. Diagrammatic representation of the mechanism of altered direction of inscription of the horizontal projection of the QRS loop in right ventricular enlargement. *A* represents a horizontal plane section of the normal heart, and *B* illustrates right ventricular hypertrophy. Excitation fronts are represented by the dotted lines *ab* and *a'b'*, and vectors *1* and *2* by which the electrocardiographic effects of these fronts can be represented are shown. Note that the effect of right ventricular enlargement has been to alter the direction of the vector toward the right. *C* shows diagrammatic horizontal plane QRS loops; *a*, *b*, and *d* are the initial limbs, and *c* is the terminal limb common to all. The loop with the initial limb *a* represents the normal horizontal plane projection of the QRS loop. An alteration in the position of some of the vectors making up the efferent limb in the direction which has been illustrated in *A* and *B* of this figure results in decreased area of the loop whose initial limb is labeled *b*, and in reversed direction of inscription in the loop whose initial limb is labeled *d*. For the purpose of clarity, the effects of right ventricular hypertrophy are shown in this illustration as affecting the position of the efferent limb only. As described in the text, the actual effect of right ventricular enlargement on the derived QRS loops was more complex and consisted of a change in the direction of vectors as illustrated in this figure but involving only mid-temporal portions of the loop.

in normal counterclockwise inscription of the QRS loop in the horizontal plane.

R′ PATTERN IN LEAD V_1 AND/OR LEAD V_2. Although detailed derivation of precordial leads from vectorcardiograms was not carried out, there were situations in which the gross features of the VCG made it likely that an R′ pattern in Lead V_1 and/or Lead V_2 would have occurred. These included the combination of right ventricular dilatation and generalized or localized hypertrophy of this chamber. Localized hypertrophy of the outflow tract even without dilatation resulted in similar findings but with a different basis. Three features of the vectorcardiograms associated with combined dilatation and hypertrophy were pertinent to the occurrence of an R′ pattern. These were: (1) forward displacement of the initial part of the efferent limb, (2) small vectors, with a tendency of the loop to return to the isoelectric point during its mid-temporal portion, and (3) rightward displacement of late vectors. The forward displacement of the initial part of the efferent limb was the direct result of ventricular dilatation, as has been described in the preceding section and illustrated in Fig. 3. Small vectors which resulted in the location of the mid-temporal portions of the loop near the isoelectric point in the horizontal plane were the result of excitation fronts essentially surrounding ventricular cavities in horizontal plane sections of the heart. These wave fronts gave little external evidence of electrical activity in the horizontal plane. Rightward displacement of late vectors occurred because right ventricular dilatation and a given degree of thickening of the wall represent a greater right ventricular mass than the same degree of hypertrophy alone. Even though the same conduction velocity was assumed in both situations, asymmetrical wave fronts approaching the right ventricular surface were longer in the case of combined dilatation and hypertrophy than in the case of hypertrophy alone. This resulted in vectors relatively late in the excitation process which were directed toward the right to a greater degree than were those which were associated with hypertrophy alone. Hypertrophy of the outflow tract also resulted in vectorcardiographic findings appropriate to result in an R′ pattern in Lead V_1 and/or Lead V_2, but a different mechanism was responsible. Early vectors were the same as those in the normal heart, but later portions of the loop were now influenced by activation in the outflow tract, without the simultaneous effect of activation in the remainder of the right ventricle, as would have occurred with generalized right ventricular hypertrophy. This had the effect of displacing a part of the afferent limb of the loop farther rightward and an-

teriorly than occurred with generalized hypertrophy or hypertrophy of the inflow tract.

POSTERIOR DISPLACEMENT OF THE VCG DUE TO RIGHT VENTRICULAR ENLARGEMENT. Generalized hypertrophy and hypertrophy localized to the free wall or to the inflow tract displaced the loop toward the right and posteriorly. Thus, these forms of hypertrophy appeared less likely to result in R′ wave patterns in Lead V_1 and/or Lead V_2 than did dilatation plus hypertrophy or hypertrophy localized to the outflow tract. Posterior displacement of the loop was especially marked in localized enlargement of the inflow tract, because activation in this portion of the hypertrophied ventricle was not balanced by simultaneous activation in the more anteriorly placed outflow tract. A diagrammatic representation of the anatomic basis of these findings is shown in *C* and *D* of Fig. 3. Electrocardiograms with deep S waves in precordial Leads V_1 through V_3 have been reported in cases of right ventricular enlargement, and the present investigation furnishes a possible explanation of these findings.[8]

RIGHT BUNDLE BRANCH BLOCK. Electrocardiograms and vectorcardiograms derived from the excitation sequence in experimental right bundle branch block had the features known to be associated with this conduction disorder in patients. The terminal portion of the QRS loop was inscribed slowly and was located to the right of the isoelectric point. This portion of the loop resulted in a wide, deep S wave in the derived Lead I and was appropriate to result in an R′ wave in Lead V_1 and/or Lead V_2, as occurs in patients with right bundle branch block. The direction of inscription of the horizontal plane projection of the QRS loop was counterclockwise. Only the terminal portion of the afferent limb was grossly altered by this conduction disorder. The normal left septal excitation, directed, first, rightward and anteriorly, and, later, left ventricular activation, directed leftward and posteriorly, resulted in a horizontal plane projection of the QRS loop inscribed in the normal counterclockwise direction.

Clinical studies. As expected from previous studies, a variety of electrocardiographic and vectorcardiographic findings were encountered in patients with right ventricular enlargement. These findings included various degrees of right axis deviation, rightward deviation of the QRS loop, large R waves or R′ patterns in Lead V_1 and/or Lead V_2, and nonspecific abnormalities of the S-T segments and T waves. The merits and limitations of these findings as diagnostic evidence of right ventricular enlargement have been considered in many reports and will not be described in detail.

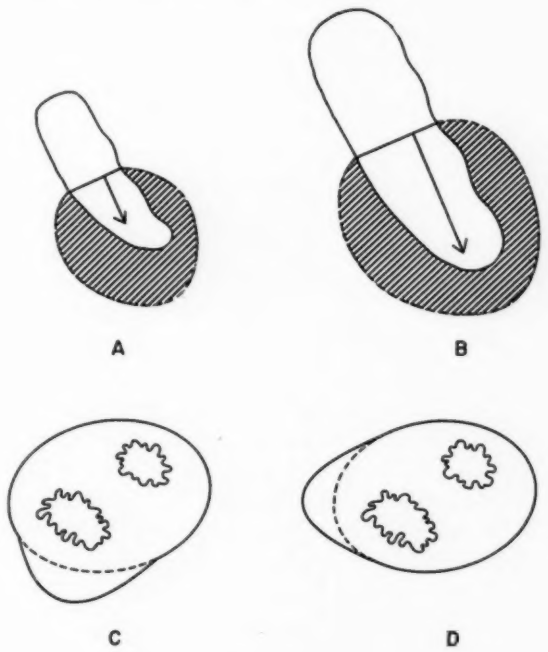

Fig. 3. *A* and *B* illustrate diagrammatically the mechanism of anterior displacement of early portions of the QRS loop by right ventricular dilatation. *A* represents the right ventricular cavity viewed in the horizontal plane, with the adjacent shaded area representing activated right ventricular muscle. The anteriorly directed vector by which this excitation moment can be represented is shown perpendicular to a line connecting the interrupted edges of the excitation front. In *B*, a similar diagram of a dilated right ventricular cavity is illustrated. Excitation has been extended over a greater portion of the endocardial surface, and a larger anteriorly directed vector is necessary to represent this excitation moment. The anatomic basis for different ECG and VCG effects of enlargement of the outflow and inflow tracts is illustrated in *C* and *D*. In these diagrammatic horizontal plane sections of the heart the lower edge represents the anterior wall. *C* illustrates hypertrophy of the outflow tract. Hypertrophy of the inflow tract is shown in *D*. Excitation fronts extending into the more anteriorly placed outflow tract resulted in greater anterior displacement of vectors by which these fronts could be represented.

The theoretical portion of this study provided several insights into the possible mechanism of some of the ECG and VCG manifestations of right ventricular enlargement and suggested certain parameters which may be useful in the differential diagnosis of the type of enlargement. The differential value of these parameters could not be evaluated in the present clinical study, since pathologic demonstration of the type of enlargement present would be necessary for such an evaluation. One method of analysis of the VCG, which the theoretical studies suggested as promising for the recognition of right ventricular hypertrophy, was appropriate to the present study and was evaluated in detail. The theoretical finding that hypertrophy sometimes alters the direction of inscription of the QRS in the horizontal plane, and at other times decreases the area of this loop without altering the direction of inscription, suggested that a quantitative parameter incorporating both direction of inscription and area of the loop might be useful in the recognition of right ventricular hypertrophy. The "polar vector" is a quantity with these characteristics and was calculated as described in the section on methods. In this series there was no significant difference between the normal records and those of patients with right ventricular enlargement in the mean values of the "polar-vector" magnitude and the angle ϕ, although there was a greater range of variation of both calculated from records of patients with enlargement. The values of ψ, however, were significantly different in the right ventricular enlargement and normal groups. In the normal group the average value of ψ was 36 degrees, and in the records of patients with enlargement the value was 97 degrees. The range of variation in the normal records was 13 to 72 degrees (standard deviation of 13 degrees), with all but two values being less than 55 degrees. In the right ventricular enlargement group the range was 33 to 161 degrees (standard deviation of 35 degrees), with all but two records having a value greater than 55 degrees. These records included those from 19 patients whose electrocardiograms did not fulfill Milnor's criteria for right ventricular enlargement. When these latter patients were considered as a group, there was still a highly significant difference between the values of ψ for this group and the values for the normal group.

Discussion

It should be emphasized that the theoretical studies reported were carried out only to furnish insight into the possible mechanism of electrocardiographic and vectorcardiographic manifestations of right ventricular enlargement. Evaluation of the usefulness of specific parameters in the recognition of various types of right ventricular enlargement will require combined clinical and pathologic studies. The clinical portion of the present investigation supports the usefulness of one parameter, namely, the "polar vector" as an index of right ventricular hypertrophy. This quantity differed significantly between normal records and those of patients with right ventricular enlargement, including several patients without currently accepted electrocardiographic evidence of that lesion.

The theoretical studies had definite limitations and necessitated several simplifying assumptions. These include consideration of excitation at only a limited number of moments and at a limited number of anatomic levels. They also include the assumptions that standard ECG leads represent projections of the frontal plane loop on the sides of an equilateral triangle, and that vectorcardiograms represent projections on a perfect orthogonal lead system. It was also necessary to postulate the excitation sequence in enlarged portions of the right ventricle, since direct studies of the excitation order in this situation have not been carried out. Despite these limitations and assumptions, the theoretical approach appeared to be worth while, since it is extremely difficult to be certain that right ventricular enlargement is not associated with a conduction disorder in either experimental or clinical situations. In this study it was possible to postulate ventricular enlargement and retain the normal excitation sequence and to contrast the effects of this lesion alone with those of right bundle branch block.

It was recognized that the insights provided by the theoretical studies require clinical and pathologic evaluation. The results of the theoretical studies correlated

well with the limited clinical observations in the present study. They provided a theoretical basis for the finding that the normal direction of inscription of the QRS loop in the horizontal plane is sometimes altered by right ventricular enlargement. This alteration was the result of disproportionate effect of hypertrophy on the position of the mid-temporal portion of the loop as compared to the initial and terminal portions. The studies also indicated that slight or moderate degrees of hypertrophy might be expected to decrease the area of the horizontal plane projection of the QRS loop without actually altering the direction of inscription. This was also the result of greater effect on the position of the mid-temporal portion of the loop. These findings made it appear that the "polar vector" determined from the area of plane projections of the loop and its direction of inscription might be a valuable index of right ventricular enlargement, and the clinical portion of this study supported this possibility.

The theoretical studies also suggested several parameters which may be useful in the differential diagnosis of the type of enlargement present. The possible value of these could not be evaluated in the clinical portion of this study since this would require pathologic demonstration of the type of enlargement present, but the features with possible differential value were as follows. (1) Clockwise direction of inscription or decreased area of the horizontal plane projection of the QRS loop was a manifestation of all types of enlargement studied but was less marked with dilatation than with hypertrophy of the right ventricle. (2) The amount of anterior extension of the initial limb of the QRS loop was increased by dilatation but not by hypertrophy. (3) Vectorcardiographic features likely to be associated with an R′ pattern in Lead V_1 and/or Lead V_2 occurred with combined dilatation and hypertrophy of all varieties studied and with isolated hypertrophy of the outflow tract but not with other types of hypertrophy. (4) Posterior displacement of the QRS loop likely to be associated with deep S waves in the precordial leads was especially marked with isolated hypertrophy of the right ventricular inflow tract. Further clinical study, together with pathologic demonstration of the variety of enlargement present, will be necessary to evaluate the possible differential diagnostic value of these findings.

Summary

A theoretical study in which the electrocardiographic and vectorcardiographic effects of right bundle branch block and of several varieties of right ventricular enlargement were examined was carried out. The basis of this study was derivation of electrocardiograms and vectorcardiograms from the ventricular excitation sequence. Results of the study provided a theoretical basis for the observation that right ventricular enlargement may alter the direction of inscription of the QRS loop in the horizontal plane. Results also indicated that right ventricular enlargement may decrease the area of projection of the QRS loop in the horizontal plane without changing the direction of inscription. On the basis of these results a quantitative parameter, the "polar vector," based on the area of plane projections of the VCG and their direction of inscription, was examined in records from a group of normal subjects and records from patients with right ventricular enlargement. Results of this clinical study showed a significant difference in the orientation of this vector in records from normal subjects and those with right ventricular enlargement. The group studied included several patients whose conventional electrocardiograms were not diagnostic of right ventricular enlargement.

The theoretical study also suggested several ECG and VCG features of possible value for identifying specific varieties of right ventricular enlargement. These have not been evaluated clinically since this will require demonstration of the type of enlargement present.

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Toxicity of Coomassie blue

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Coomassie blue has recently been advocated as a suitable dye for indicator-dilution studies.[1,2] It is especially suitable for repeated injection since the level in blood falls much more rapidly than with Evans blue, and the subject does not remain blue for many days. Preliminary animal studies[1] showed that Coomassie blue was even less toxic than was Evans blue, and initial reports of its use in man confirmed the absence of toxicity in doses of 20 to 1,000 mg.; one subject received 2,000 mg. in 24 hours without ill effect.[2]

We wish to report here 3 severe pyrogenic reactions in 2 healthy people (ourselves) who received large amounts of Coomassie blue on 3 separate occasions to verify the response characteristics of an ear oximeter.

a. Injection of 450 mg. in 7 doses was given over a 5-hour period; 300 mg. were given in the last 2 hours.

b. Injections of 40, 48, 78, 168, 188, and 276 mg. were given at 9-minute intervals; a total of 798 mg. was given in 54 minutes, and the maximum blood level reached was 99.5 mg. per liter.

c. Injections of 40, 36, 72, 161, 186, 194, and 235 mg. of dye were given at 9-minute intervals; a total of 924 mg. was given in 63 minutes, and the maximum blood level reached was 138.5 mg. per liter.

On each occasion there was a period of 2 to 3 hours of well-being after the last injection. This was followed by vague malaise, which lasted 10 to 15 minutes, and then by rigors, with fever up to 104°F. (40°C.), marked hyperesthesia of skin and muscle, nausea, and vomiting, and (once) diarrhea. Blue dye was noted in the vomitus and diarrhea fluid; this is in keeping with its known elimination in the bile.[1] No pain in the joints, effusions, rash, bronchospasm, or abdominal pains were noted. The fever and symptoms slowly subsided over the course of 5 or 6 hours—once after 600 mg. of acetylsalicylic acid per os and twice after 50 mg. of diphenhydramine hydrochloride (Benadryl) intramuscularly; we do not know whether this treatment altered the natural course of the illness. Minor episodes of sweating with low-grade fever occurred for 2 or 3 days more, but no other sequelae were noted. Blood cultures taken during a rigor were sterile each time, and the total and differential leukocyte counts were normal.

Since that time, the same subjects have received smaller amounts of dye without ill

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effect; the maximum blood levels, however, have been much lower than during these reactions. On one occasion, 8 injections of 54 mg. were given over 8 hours, with a maximum blood level of 8.9 mg. per liter. Many other subjects have had 6 injections of 50 mg. over 4 to 5 hours, with no adverse reactions.

The cause of the pyrogenic reaction has not yet been found; it is clearly related to high blood and/or tissue levels. No evidence of particulate matter was detected on microscopy of plasma containing 200 mg. per liter of dye, nor was any detected in the dye itself by bacterial filters. The clinical course is unlike that due to a bacterial pyrogen.[3] The unusual latent period must be of significance, and it should be noted that after accidental perivenous injection of the dye, severe pain ensued after a time interval of similar duration. Further studies into the mechanism are being made by workers at the Imperial Chemical Industries in the United Kingdom.[4]

It should be stressed that low doses of Coomassie blue can be used safely; within this limitation it remains a valuable agent for studies involving frequent indicator-dilution curves.

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Vectorcardiographic deflections obtained with various reference systems in cadavers

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Many systems of electrode placement have been proposed and are being used for spatial vectorcardiography. Some of these are based on carefully controlled experiments on torso models. This report is concerned with results of similar experiments on fresh cadavers through the use of some popular vectorcardiographic reference systems.

Methods

Needle electrodes, insulated except at the tips, were assembled in a Lucite base, as shown in Fig. 1. The electrodes were inserted through the chest into the heart of the fresh cadaver (2 to 6 hours post mortem) and appropriately supplied with a 20-cycle current. These electrodes constituted artificial dipoles which were orthogonally oriented horizontally, vertically, and front to back, and at 45° angles to both frontal and sagittal planes (pointing anteriorly, inferiorly, and toward the left of the body). Separate similar electrode arrangements without fixation to a Lucite base were also inserted directly into the exposed heart, and then the chest was closed for the study. Individual lead boxes permitted rapid transfer of the amplifiers and cathode-ray tubes for frontal and left sagittal display from electrodes located

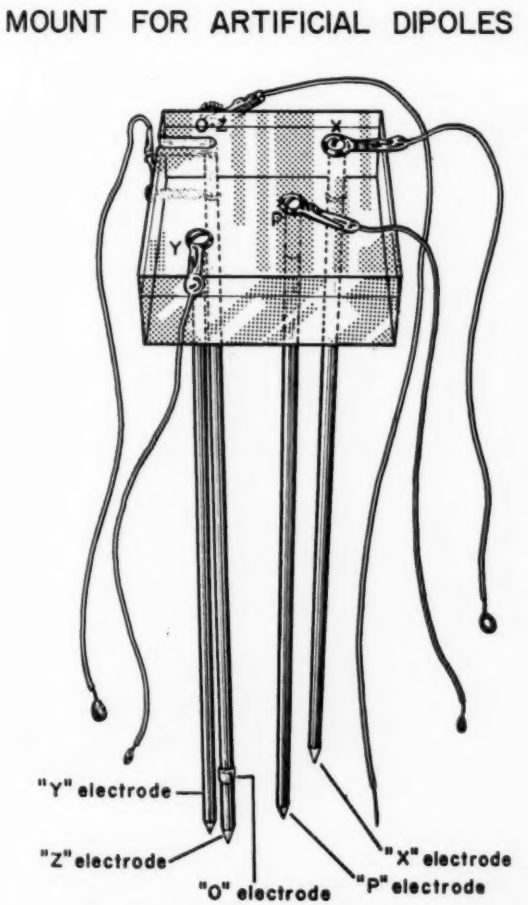

Fig. *1*. The electrodes used for the pseudo-dipoles which were inserted into the heart through the anterior chest wall of 15 intact cadavers.

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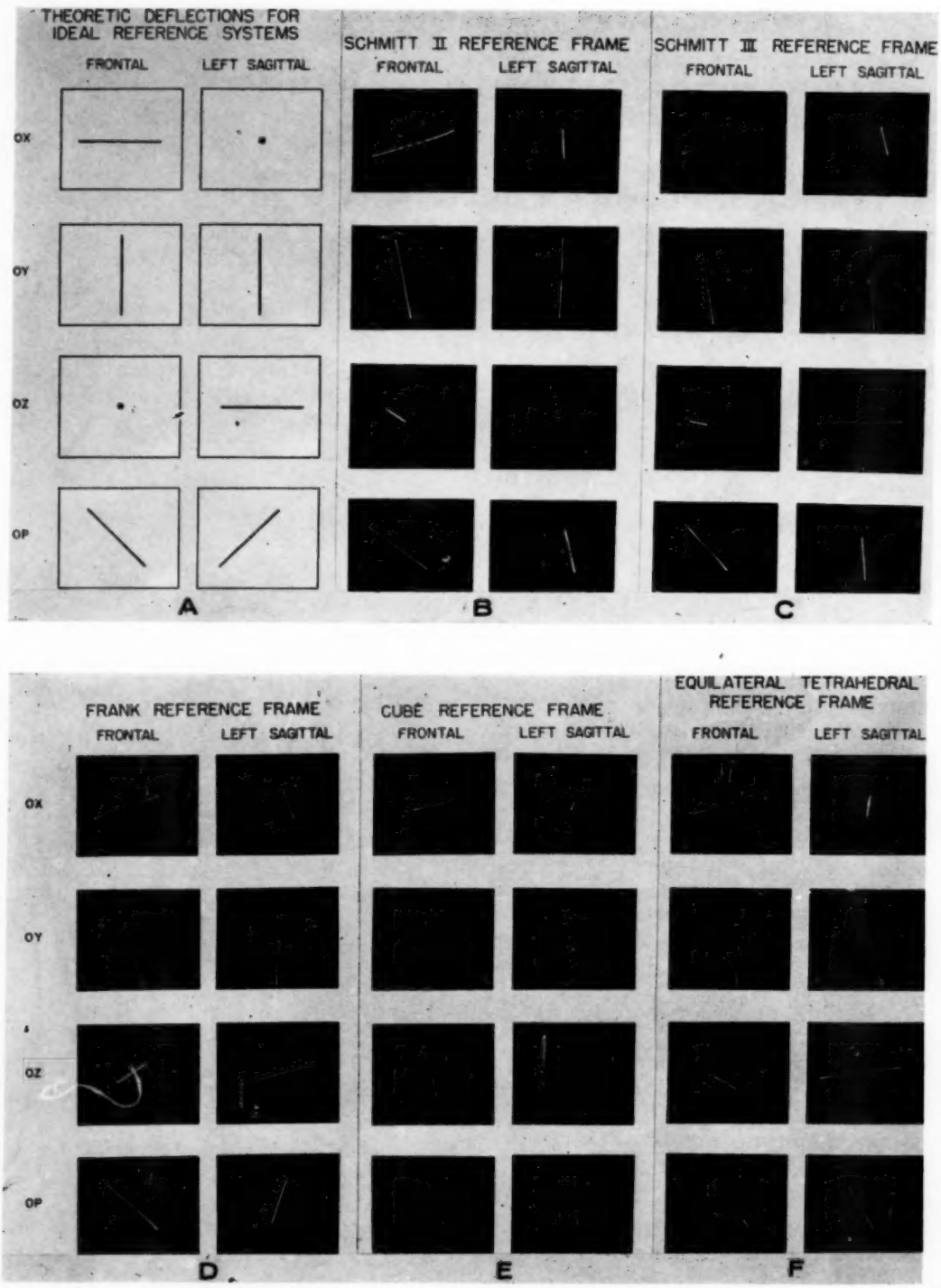

Fig. 2. *A*, The theoretical deflections that would be obtained in the frontal and left sagittal plane projections for ideal reference systems and dipole orientation. *OX* is parallel to the horizontal in the frontal plane. *OY* is parallel to the vertical in the frontal plane. *OZ* is perpendicular to the frontal plane. *OP* is at an angle of 45° to the frontal and sagittal planes. *B*, Typical recording obtained from a cadaver for the frontal and left sagittal plane projections with the Schmitt-II method of electrode placement. The recordings shown in *B* through *F* were obtained for the same cadaver and the same artificial dipoles. *C*, Typical recording obtained from the cadaver for the frontal and left sagittal plane projections with the Schmitt-III method of electrode placement. *D*, Typical recording obtained from the cadaver for the frontal and left sagittal plane projections with Frank method of electrode placement. *E*, Typical recording obtained from the cadaver for the frontal and left sagittal plane projections with the cube method of electrode placement. *F*, Typical recording obtained from the cadaver for the frontal and left sagittal plane projections with the equilateral tetrahedral method of electrode placement.

according to the Schmitt II,[1] Schmitt III,[1] simplified Frank,[2] cube,[3] and Wilson's equilateral tetrahedral[4] systems. The Burger system was not studied because of the difficulty of adapting the equipment to that system. Time limitation on each experiment imposed by the pathologist also restricted the number of systems which could be studied on each body. Two-dimensional roentgenograms and subsequent opening of the chest permitted determination of the actual spatial position of the dipole electrodes in the heart. In each experiment the recommended amplifier standardization was employed, and the dipole current was constant.

Results

Experiments were performed on 15 cadavers. If penetration of the heart muscle by the dipole electrodes was not satisfactorily obtained, the observations were discarded. The results obtained from the various satisfactory experiments for the respective reference systems studied are typified by Fig. 2, *B-F*. The theoretically correct vectorcardiographic directions are shown in Fig. 2,*A*.

Discussion

The difficulty of achieving truly symmetrical electrode placement in this experiment is realized. Variable contact resistance around the periphery of the electrodes and improper implantation of the electrodes in the heart muscle are among the technical factors which may have modified the effective dipole direction from the physical direction between the electrodes. In any case, all of the chosen vectorcardiographic systems were tested with the same pseudo-dipoles. The variations in recorded directions and magnitudes for presumably the same views of the dipoles indicate that none of the systems tested were completely satisfactory.

The pseudo-dipole electrodes in the heart of the cadavers probably were not spatially oriented as precisely as desired, but once they were in place, they were used for all the reference systems investigated. Thus, if each reference system were ideal, the recorded deflections would have been the same for all systems.

Although the fresh cadaver is different from a living man, such an experimental model resembles the living intact man more closely than does an artificial torso model.

Summary

A study of artificially applied dipoles in the heart of fresh cadavers clearly showed that some systems of electrode placement employed for spatial vectorcardiography are far from perfect.

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Precordial low-frequency displacements of the thoracic wall
Method of recording and registration

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The recording and registration of low-frequency precordial movements of the chest wall caused by cardiac action have become the focus of increasing attention in the past few decades. In this connection, we may refer to publications by Johnston and Overy,[6] in which is presented a survey of results obtained up to 1951, with their interpretation.

Continuing this line of investigation, Eddleman,[8-10,12] Luisada,[7] Groom and Elliott,[11] with their respective co-workers, have developed recording methods which have contributed to our knowledge of precordial movements of the chest wall. For this purpose, Eddleman made use of the fact that mechanical fluctuations in pressure can be piezoelectrically converted into electrical signals. Luisada recorded precordial movements of the chest wall with the aid of a contact crystal microphone. Groom used the electronic pick-up RCA 5734—the triode with the moving anode. Elliott used the accelerometer, based on the principle of electrocapillarity.

For the same purpose, we have used the Philips displacement meter and transducer, based on the principle of the differential transformer.

Method

If mechanical quantities are measured by electrical methods, then the apparatus required can be divided into two parts, i.e., (a) the transducer, with which the mechanical quantity is converted into an electrical quantity, and (b) the measuring apparatus, with which the electrical quantity is amplified and measured.

The transducer. The transducer PR 9310/01 is an instrument with a length of 5.3 cm. and a diameter of 2.3 cm. (transverse section shown in Fig. 1). It consists of a steel casing (*A*) with a copper lining (*B*), from which a needle (*K*) protrudes; we fixed a globule of resin (*E*) with a diameter of 1 mm. onto the end of this protruding needle. The center of the needle contains a small ferromagnetic core (*H*). Both the needle and the core are movable in axial direction in a tube (not magnetizable within the steel casing) on which one primary (*C*) and two secondary coils (*G*) have been mounted.

The axial movement of the core of the measuring needle results in a change in the coupling of each of the two secondary coils with the primary coil; as a result, the voltages induced in the secondary coils

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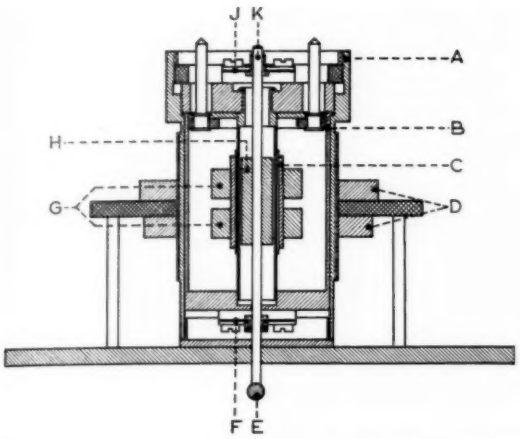

Fig. *1.* Transverse section of the transducer and plastic holder (ϕ6 cm.)

are opposed. The ensuing difference in voltage can be determined with the aid of a suitable measuring apparatus, connected with the transducer by means of a measuring cable, 5 M. in length.

The coil system of the transducer is electrically screened off by means of the copper lining inside the steel casing. The induced voltages, therefore, are not influenced either by the metal holder into which the instrument may be built or by static fields in the vicinity.

The primary coil is fed a stabilized alternating current (2.75 volts effective at 30 Ma., 4,000 Herz.).

With the aid of adjusting nuts (*D*), the entire system was mounted in an adjustable plastic holder (ϕ 6 cm.) which can be attached to the patient by means of a rubber band, so that the measuring needle can be applied to any desired site on the thorax. In this way, the investigator's interference with registration, as well as the influence of respiration, are avoided, as are also minor displacements of the patient relative to a transducer not attached to the patient. The displacement of the rim of the holder is small in comparison to the displacement of the probe.

The mass of the moving system amounts to 1 gram, and this implies that the influence on the object to be measured is inconsiderable. The measuring needle of the transducer is subject to outward pressure exerted by bearing springs (*F,J*), with a force which amounts to about 2×10^4 dynes in the central position. The spring rigidity is 15×10^4 dynes per centimeter. During use, the measuring needle must not be subjected to transverse stress, i.e., stress perpendicular to the longitudinal axis.

The maximal deflection, i.e., the permissible deflection longitudinally to either side

Fig. *2. Left*: Transducer fixed on the patient. *Center:* Hellige recorder and the cathode-ray tube. *Right:* Measuring apparatus.

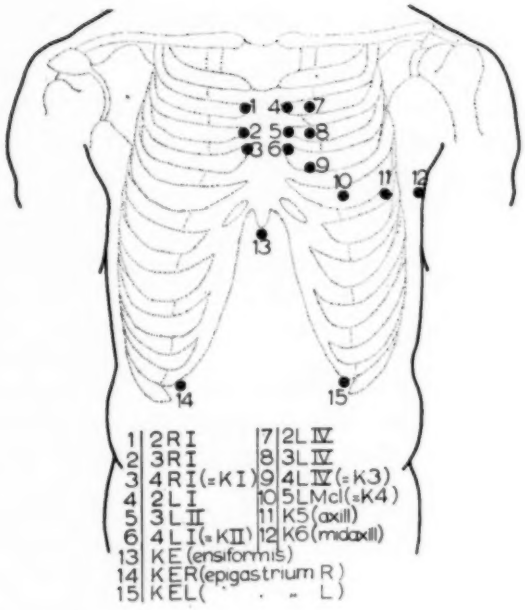

Fig. 3. See text.

of the central position of the measuring needle, is 1 mm. Overloading of the measuring apparatus occurs after larger displacements of the chest wall. The apparatus is capable of measuring, independently, vibrations ranging from frequency 0 cycles per second to frequency 70 cycles per second (independent of amplitude); a reproducible and proportionate recording of the displacement of the chest wall is thus ensured. The sensitivity is 0.25 mv./μm.

It should be pointed out that the output voltage emitted is proportionate to the displacement instead of to the velocity, as in the case of electromagnetic and electrodynamic recorders.

The measuring apparatus. The measuring bridge, which can be regarded as a bridge of wheatstone, is the most important part of the measuring apparatus (PR 9300).* This bridge, combined with the transducer described in the previous section, makes it possible to measure the displacements of the measuring needle.

It is possible to adjust the apparatus to the following six measuring ranges, which differ by a factor of 3: from +3 to −3 μm; +10 to −10 μm; +30 to −30 μm; +100 to −100 μm; +300 to −300 μm; +1,000 to −1,000 μm.

The values for slow fluctuations of the chest wall, e.g., due to respiration, can be read directly from a dial instrument (continuous-current microamperemeter with 500 microamperes at full dial deflection). In our experiments, this instrument was used only for orientation as to measuring limits.

After adjustment, observations were made with the aid of a cathode-ray tube for visual evaluation, and the recording with a four-channel photographic Hellige apparatus. The output of the measuring apparatus, it was found, could be readily adapted to the final stage of the above-mentioned Hellige apparatus. Recordings were made synchronously with heart sounds and electrocardiographic findings.

If desirable, a segment of the displacement curve with high sensitivity can be studied in detail while the remainder of the curve is overloaded.

Application to the patient. The above-described apparatus is set up, and the transducer attached to the chest of the

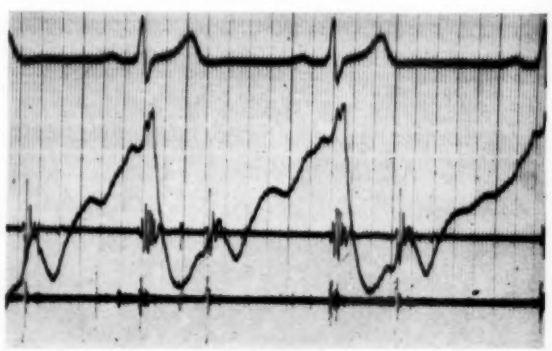

Fig. 4. Kinetocardiogram: (2R1) = K_{12}. Measuring range: +10 μm to −10 μm. ECG: Lead II. Phonocardiogram: Apical sounds. Speed of paper: 50 mm. per second.

Fig. 5. Kinetocardiogram: (3R1) = K_{13}. Measuring range, ECG, phonocardiogram, and paper speed are the same as for Fig. 4.

*PR 9300 = Serial number of Philips Electronics.

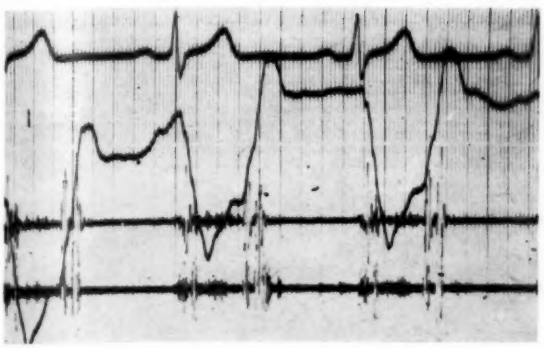

Fig. *6*. Kinetocardiogram: (4R1) = K_{14}. Phonocardiogram: Sounds 2L1. Measuring range, ECG, and paper speed are the same as for Fig. 4.

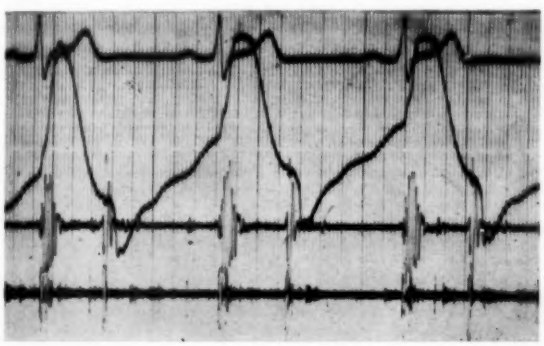

Fig. *7*. Kinetocardiogram: (2L1) = K_{22}. Measuring range: +30 μm to −30 μm. ECG: Lead II. Phonocardiogram: Apical sounds. Speed of paper: 50 mm. per second.

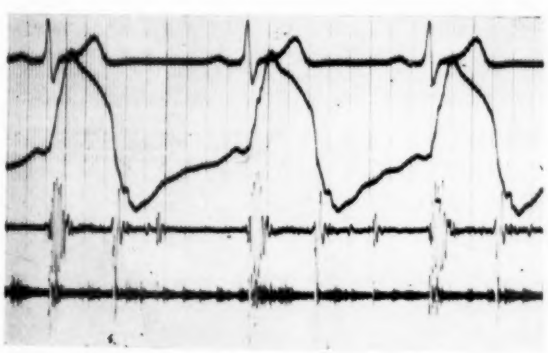

Fig. *8*. Kinetocardiogram: (3L1) = K_{23}. Measuring range, ECG, phonocardiogram, and paper speed are the same as for Fig. 7.

subject under examination, in the manner demonstrated in Fig. 2. It is ascertained that the measuring needle of the transducer is localized at the exact site on the chest wall at which precordial movements are to be measured; the transducer with the measuring needle can be shifted in the holder (by means of a fine-pitched screw thread) in such a way that the measuring needle itself is in the central position perpendicular to the chest wall. This last point can be checked against the position of the dial on the scale of the measuring apparatus. At the same time, the electrodes for the electrocardiogram are applied, and in a number of cases, for reference, heart sounds are simultaneously recorded elsewhere on the chest wall.

It must be borne in mind that the mass of the heart-sound microphone may influence recording when an attempt is made to derive both phenomena too close together, with the measuring apparatus in a sensitive measuring position.

We carried out recordings with the patient in deep expiration, holding his breath.

Results

Fig. 3 shows the sites on the precordium, and elsewhere, at which we recorded precordial movements or their derivations.

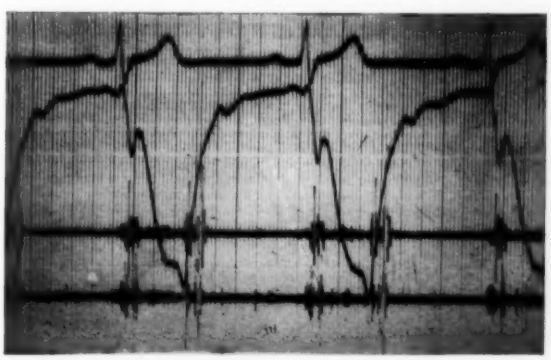

Fig. *9*. Kinetocardiogram: (4L1) = K_{24}. Measuring range: +30 μm to −30 μm. ECG: Lead II. Phonocardiogram: Sounds 2L1. Speed of paper: 50 mm. per second.

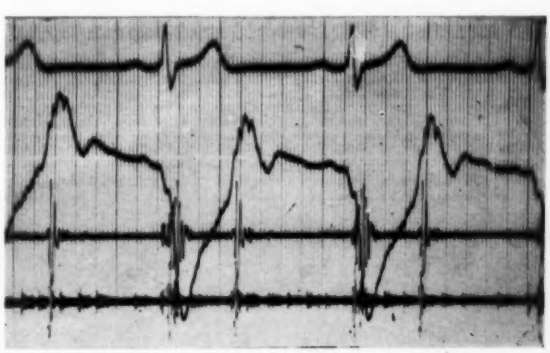

Fig. *10*. Kinetocardiogram: (2L4) = K_{32}. Measuring range, ECG, phonocardiogram, and paper speed are the same as for Fig. 7.

Wherever these sites corresponded with those also used by Eddleman, we inserted the Eddleman designations of K (kinetocardiogram) with corresponding numeral.

Obviously, the small integrating surface of the transducer makes it possible to enlarge the field of derivation points at will and explore the entire precordium in this manner, which ensures excellent curves illustrating the course.

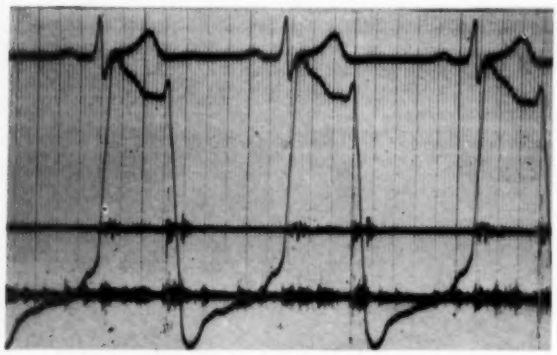

Fig. *11.* Kinetocardiogram: (3L4) = K_{33}. Curve obtained proves ictus of right ventricle. Measuring range: +30 μm to −30 μm. ECG: Lead II. Phonocardiogram: Sounds 2R1. Speed of paper: 50 mm. per second

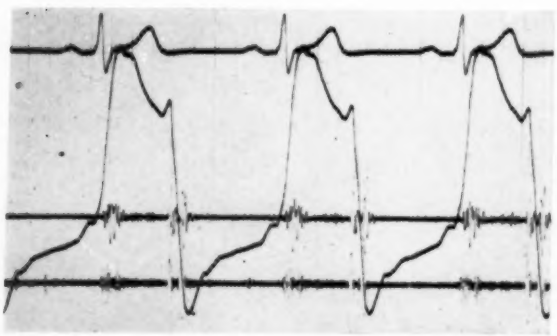

Fig. *12.* Kinetocardiogram: Left ictus, dorsal recumbent position. Measuring range: +50 μm to −50 μm. ECG: Lead II. Phonocardiogram: 2R1. Speed of paper: 50 mm. per second.

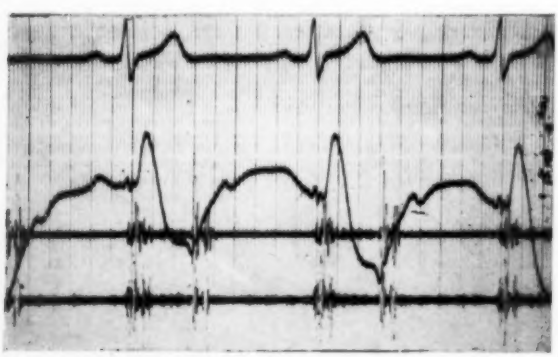

Fig. *13.* Kinetocardiogram: K_{34}. Measuring range, ECG, phonocardiogram, and paper speed are the same as for Fig. 11.

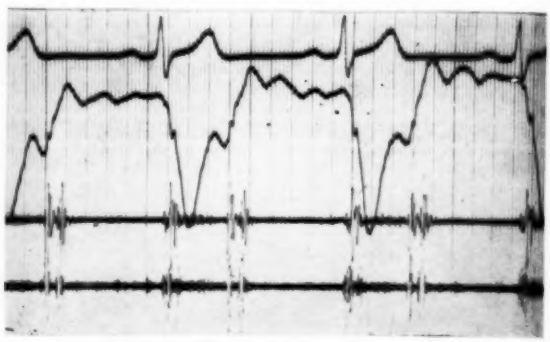

Fig. *14.* Kinetocardiogram: K_{54}. Measuring range: +10 μm to −10 μm. ECG: Lead II. Phonocardiogram: Sounds 2L1. Speed of paper: 50 mm. per second.

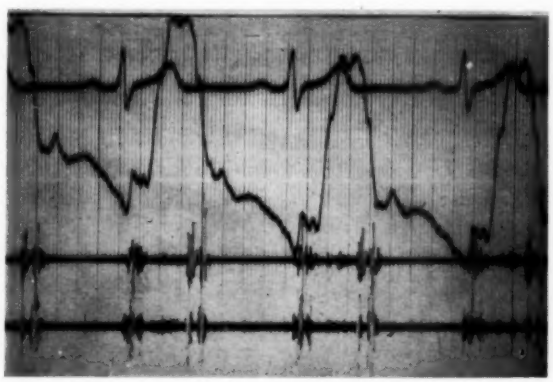

Fig. *15.* Kinetocardiogram: K ensiform. Measuring range, ECG, phonocardiogram, and paper speed are the same as for Fig. 14.

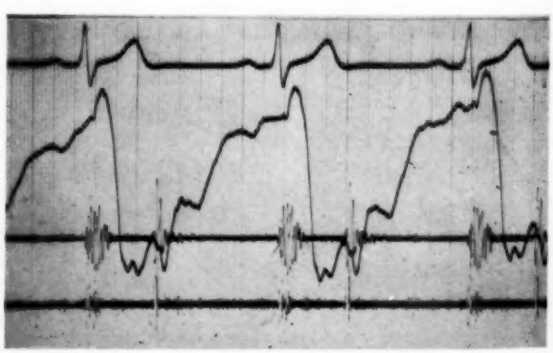

Fig. *16.* Kinetocardiogram: Mid-clavicular 1R epigastrium. Measuring range, ECG, phonocardiogram, and paper speed are the same as for Fig. 14.

Figs. 4 through 16 present a few results obtained by this method of registration in a 13-year-old male patient.

A detailed discussion or explanation of the illustrations is not within the scope of this paper.

Summary

1. A description is given of a new method of recording precordial movements of the chest wall, with illustrations depicting the apparatus and the mode of application to the subject to be examined. A number of curves obtained by this method are presented in addition.

2. The authors believe that the new method offers the following advantages over conventional recording methods: (a) small integrating surface of the transducer, as a result of which precordial displacements of the chest wall are locally measured, whereas other transducers measure a contribution from several precordial sites; (b) proportional and reproducible recording of precordial displacements caused by the heart action; (c) instant registration, frequency range, and high sensitivity because of the physical characteristics of the transducer and the measuring apparatus.

3. Results and interpretations obtained from hearts with a normal and a pathophysiologic function will be presented in a subsequent publication.

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Arterial volume and pressure pulse contours in the young human subject

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The dynamics of blood flow in peripheral arteries have been a subject of intense study since the original publication of Poiseuille and Frank. Otto Frank's main interest[1] centered on the problem of propagation of pressure waves in elastic tubes, but he also recognized the problem of propagation of wall vibrations, as independent of that of pressure transmission. Subsequently, in the voluminous literature on the transmission of pulse waves, definite distinction has not always been made between volume pulses and pressure pulses, and recordings of changes in vessel diameter have been used to discuss the properties of pressure pulses. Although under normal conditions, local increase in arterial capacity is a reliable index of the degree of elevation in intraluminal pressure, under conditions of vasoconstriction or vasodilatation this may not be so; furthermore, the pressure with which volume-sensing elements are applied against the artery determines largely the size and contour of the recorded pulses, without much affecting the intra-arterial pressure.[2,3]

So far, volume pulses from arterial trunks in vivo, correlated directly with pressure pulses, have been obtained only in animal experiments, either through a mercury-in-rubber strain gauge[4] or through a differential transformer attached indirectly to the vessel.[5] Circumference has been plotted against pressure either continuously on the Y and X axes of a cathode-ray tube[4] or by feeding information received onto a tape recorder and performing automatic analog or digital computer analysis of the data.[5]

Electrical impedance plethysmography[6] offers the possibility of recording volumetric changes of arterial trunks in situ in human beings, with little discomfort to the subject. We have used an instantaneously subtracting amplifier and recorded the scalar difference of pressure minus impedance (volume) pulses; details of brachial arterial capacity versus pressure have been studied in this way in the young human subject.

Subjects and methods

Ten healthy "volunteer" male students, aged 18 to 24 years, were studied in a room with average temperature of 78° to 84° F. The subjects were examined in recumbency, and the left arm was positioned at the cardiac zero pressure level by the use of a soft arm support. The left brachial artery at the elbow was punctured with a Cournand needle which was connected with a 10-cm. or 30-cm. long *rigid* polyethylene catheter (external diameter 3 mm.,

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internal diameter 2 mm.) to a Statham P23AA gauge. The gauge output was fed into a pressure amplifier of an Electronics for Medicine recorder. The needle was flushed repeatedly with heparinized saline solution during the course of each experiment; natural frequency response of the pressure pick-up system was 35 and 50 cycles per second with the longer and shorter connecting tubes, respectively. In 3 further male volunteers the brachial and/or femoral artery was entered with a 15-gauge needle; a 25-cm. long PE-90 polyethylene catheter was introduced through it into the artery, and the needle removed thereafter; the polyethylene catheter was directly connected with the strain gauge.

Impedance changes of the artery were measured by means of a two-electrode system and a transistorized impedance plethysmograph*; this unit operates on a carrier frequency of 30 kilocycles, and the current flowing through the skin and subcutaneous electrodes is approximately 2 milliamperes (this is not perceptible by the subjects). Time constant of the impedance amplifier plus connected ECG channel of recorder was 1.5 seconds; the amplifier of the recorder channel had a frequency response flat from 0.1 to 100 cycles for second and a cut-off rate of 6 decibles per octave at each end.

The Cournand needle or the tip of the polyethylene catheter was used as one electrode; the other electrode was either a one-inch round lead disc placed on the skin (with ECG standard *paste* and adhesive tape) over the tip of the needle or catheter, or a subcutaneously inserted 21-gauge stainless steel needle (¾ inch) coated with insulating material except for its tip. The needle was inserted parallelly and as close to the artery and tip of the polyethylene catheter or Cournand needle as possible. The delay of the entire pressure pick-up system with respect to the impedance system was 0.0036 second; this delay and the frequency responses of the two recording systems were observed from transient oscillations with the needle, catheter, and electrodes connected to a saline-filled rubber tube.

*Manufactured by Parks Electronics Lab., Wheeler Ct., Aloha, Ore.

The impedance pulses were calibrated by adding into the circuit a pure resistance of 0.1 ohm; this resistance was also used to determine the time constant of the unit and connected amplifiers; in all records an increased conductance (decreased resistivity) is indicated by an upward deflection.

The impedance pulse and the pressure pulse were initially compared by connecting them with the Y and X axes of a second cathode-ray tube. Since no easy method for detailed study of their composite curve was available, in the majority of experiments the height of the impedance pulse was adjusted to equal exactly that of the pressure pulse; then, pressure pulse and impedance (volume) pulse were fed, respectively, into the plus and minus sections of a subtracting DC-amplifier. The scalar difference of the two pulses (pressure minus volume) was simultaneously recorded along with the pulses themselves and the electrocardiographic Lead II on photographic paper at a speed of 84 mm. per second. This enabled us to compare fine differences of latent periods and contour details in these amplitude-equalized pulses, which could not be done easily by simple simultaneous recording of the two pulses.

A short period of hypertension was obtained by voluntary breath-holding for 30 to 60 seconds or with the cold-pressor test. Inhalation of amyl nitrite for a few seconds was used to briefly lower the blood pressure. Recordings were taken usually at the points of maximal change in blood pressure.

Results

1. Relative delay of the pressure pulse. In most cases the foot of the pressure pulse trailed that of the impedance pulse obtained at the same point by a fairly constant interval in each individual; this was true when either the skin or subcutaneous electrode was used for the impedance pulse. This delay is evident in the tracings of the subtraction curve of the two pulses by an initial *slow* downward movement from its end-diastolic base line (Figs. 1, 2, and 3). The net mean temporal delay (recorded lag minus lag of the pressure system) of the foot of the pressure pulse with respect to that of the volume pulse at

the brachial level was 0.0104 ± 0.0127* second in these subjects; with a mean pulse wave transmission velocity of 7 meters per second, the distance between the front of the volume pulse and that of the pressure pulse must be about 7 cm. at the level of the elbow. Attempts at determining this distance by introducing a catheter upstream until the fronts of the two pulses coincided were successful only once, in the femoral artery (see Fig. 1, lower section). The distance between volume-recording and pressure-recording devices was 9.5 cm. The pressure pulse delay, previously described by Heyman,[7] who used another method for recording external pulses, varies with vasomotion; vasoconstriction decreases it and vasodilatation increases it by 5 to 8 thousandths of a second (see Fig. 3); during hypertensive periods the rise in pressure may even precede the rise in volume, as would occur in a rigid tube expanding only after a certain rise in pressure.

2. Differences between volume and pressure pulse contours. Despite the delay of its front, the pressure pulse rises faster than does the volume pulse; this is evident in the subtraction curve of the two pulses (Figs. 1 and 2), by its sudden reversal to the zero level or above it after the early negative phase. Thus, the crest of pressure is reached before that of volume.

The net mean time at which the subtraction curve reversed its course from negative to positive (equal rates of rise in volume and rise in pressure) was 0.021 ± 0.020 second; the net mean time at which the subtraction curve returned to the base line, i.e., the deflections of volume and pressure became equal, was 0.035 ± 0.027 second for the entire group of persons.

The volume systolic plateau, as a rule, lasts longer than the pressure systolic plateau; the pressure pulse has at this site a definitely peripheral character, with a narrow plateau followed by a deep notch.[8-10] As a consequence, the subtraction curve becomes negative again during the remainder of systole and approaches the zero line of difference at about the dicrotic notch. At this point also the volume curve lags behind the pressure curve, so that the over-all duration of systole in the volume pulse exceeds by 0.04 to 0.06 second that in the pressure pulse; more than half of this is due to the relative lag of the dicrotic notch in the volume pulse.

In diastole, the rebound dicrotic wave of the volume pulse is also constantly

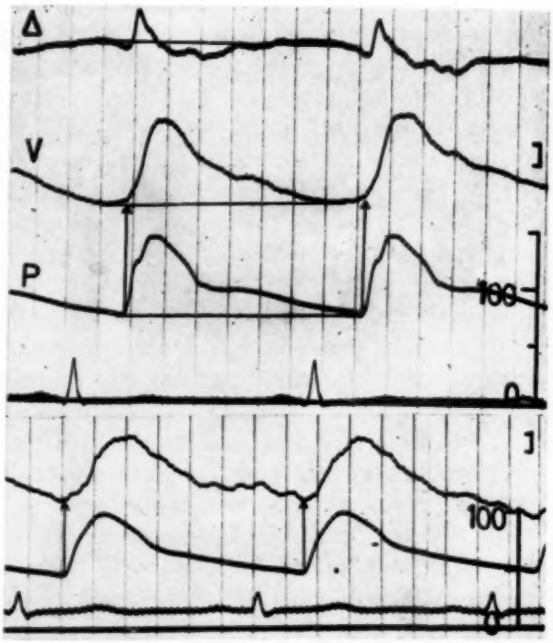

Fig. *1. Upper section:* Volume pulse (*V*) and pressure pulse (*P*) of the left femoral artery, and instantaneous difference between them (Δ), volume pulse being subtracted from the pressure pulse. Electrocardiographic Lead II coincides with the pressure base line. The pressure pulse is obtained from a 25-cm. long PE-90 tube directly connected with a P23AA gauge. The volume pulse is obtained by recording electrical impedance changes between the tip of the catheter and a 21-gauge needle located subcutaneously right over the tip of the catheter. The size of volume pulse has been adjusted so that its maximal height equals approximately that of the pressure pulse (original heights, 21.8 mm. for *V*, 20.8 mm. for *P*). The ratio of areas of the two pulses is 118:100. The arrows point at the difference in onset of the two pulses. *Lower section:* As above, but the volume pulse is obtained from two subcutaneously inserted needles on each side of the femoral artery; the pressure pulse is recorded from a 40-cm. PE-90 tube advanced 9.5 cm. up into the femoral artery, until the feet of the two pulses coincide. The heights of the two pulses are exactly equal (original heights, 17.0 mm. for both). The ratio of the two pulse areas is 125:100. The pressure pulse contour is slightly damped, because of the length of the catheter. The beat-to-beat variability of the volume pulses is obvious in both records. Calibration at the right is 0.1 ohm for impedance (volume), and 0, 50, 100, 150 mm. Hg for pressure; time in 0.1-second lines.

*Mean and standard deviation.

relatively larger than the pressure rebound dicrotic wave. Therefore, the subtraction curve becomes again negative, and slopes off to zero only at the end-diastolic period (Figs. 2 and 3). This is important, because the time constant of the volume amplifier will tend to reduce the height of the volume pulse relatively faster than does the pressure (DC) amplifier. Fluctuations in the beat-to-beat configuration of the systolic portion of the volume pulse are frequent; diastolic portions of the volume pulse display variability related chiefly to respiration.

The over-all area of the volume pulse over its diastolic level exceeds, in consequence, the comparable area of the pressure pulse when the maximal deflections are made exactly equal. The mean ratio of these two areas in several resting pulses from the 13 cases was 127.30 ± 14.97:100.00 (volume:pressure); the coefficient of variation was 11.76 per cent.

3. Impedance pulses obtained with skin and subcutaneous electrodes. The arrival times of the volume pulses obtained with the two techniques did not differ, but pulses obtained with the subcutaneous electrode tended to display small elevations of higher frequency, mainly in late diastole; these occasionally obscured the exact onset of the upstroke. Respiratory waves and base-line irregularities were more prominent with the subcutaneous electrode; furthermore, pulses obtained with this electrode were usually smaller, so that higher gain had to be used in adjustment of their height. Another, less obvious difference, was the slower run-off time of pulses with the skin electrode; this is evident in Fig. 2 by the longer duration of the second negative phase of the subtraction curve. Despite these minor qualitative differences, the areas of several volume pulses obtained with the two methods in 4 persons studied more closely did not differ once their heights were equaled.

4. Effects of vasoconstriction and vasodilatation. None of these young subjects was a hyperreactor to the cold-pressor or the breath-holding test. The delay in onset of the pressure decreased, and, on occasion, the rise in the pressure pulse preceded the rise in the volume pulse. Also, the pressure upstroke was usually accelerated, so that the net mean time at which the subtraction curve returned to the base line (return time) in 7 persons studied more closely decreased from 0.039 ± 0.018 second to 0.011 ± 0.007 second during hypertension. These differences were not statistically significant, however, when

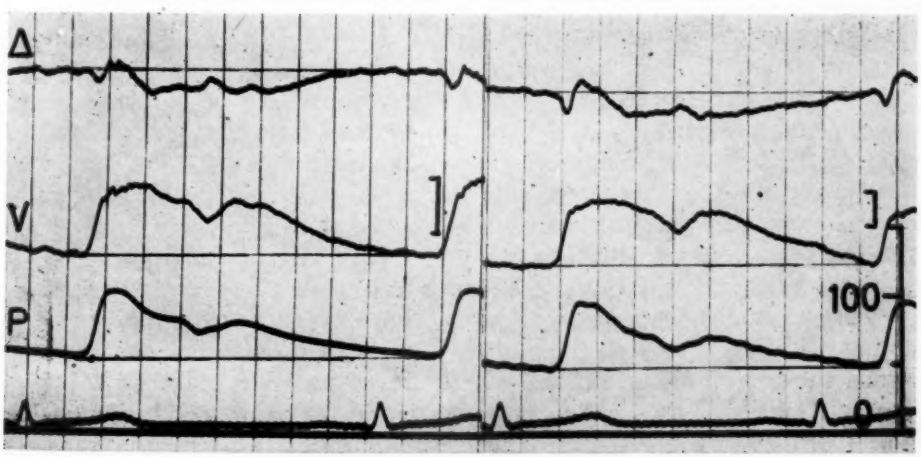

Fig. 2. Volume pulses (*V*) and pressure pulses (*P*) from the left brachial artery, and instantaneous difference between the two (Δ), with electrocardiographic Lead II. The pressure pulse is recorded with a Cournand needle connected through a 30-cm. PE-280 catheter to a P23AA gauge. The volume pulse represents impedance changes between the Cournand needle and a subcutaneous needle over its tip (*on the left*), and between the Cournand needle and a small lead electrode placed on the skin in the same location (*pulse on right*). The heights of the volume pulses have been adjusted to equal exactly those of the pressure pulses. The ratio of the areas of the two pulses on the left is 152:100; that of the pulses on the right is 155:100. Calibration and time lines as in Fig. 1.

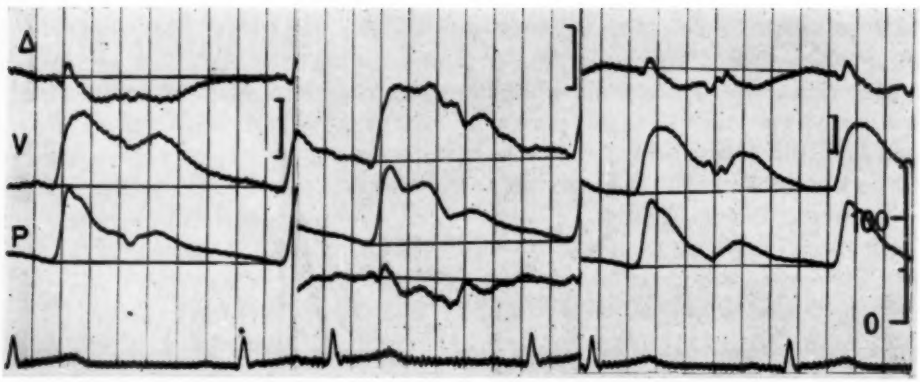

Fig. *3*. As in Fig. 2. The volume pulses are obtained between the Cournand needle and a small lead electrode on the surface over the tip of the needle. Pulses on the left are recorded under control resting conditions; the center pulses are recorded at the end of a 60-second period of breath-holding; and the pulses on the right are obtained a few seconds after inhalation of amyl nitrite. Calibration and time as in Figs. 1 and 2. Observe the different gains of the amplifier for the impedance pulses in the three sections.

paired comparisons were made, on account of an increase in return time in one case. The product-moment coefficient of correlation between the return times before and during hypertension was −0.58, indicating a weak negative correlation between these two measurements in the same individual.

Further qualitative changes in contour included a prolongation of the pressure systolic plateau and slower diastolic drop. The volume pulses changed in many respects: their size decreased, so that to obtain a deflection equal in height to that of the pressure pulse the gain had to be adjusted up by varying degrees. Furthermore, evidence of viscous properties of the wall or of "delayed compliance" of change in volume with respect to change in pressure appeared. Thus, anacrotic breaks appeared, leading to a late systolic peak of the volume pulse; the delay of the dicrotic notch (volume) became longer. In contrasting addition, the diastolic sloping off toward the base line became faster, so that the subtraction curve approached the base line or became positive in late diastole (pressure fall-off was slower than volume fall-off, starting from identical systolic heights). As a result of this, the ratio of the volume to pressure pulse areas decreased in 6 out of 7 cases; the mean ratio decreased from 124.14 to 117.57 per cent. The mean of these differences is −6.57 and its standard deviation is ±13.22. This decrease is not significant because of an increase in ratio in one of these 7 cases.

Inhalation of amyl nitrite produced an accentuation of the normal volume-pressure relations; the volume pulse increased markedly in size and preceded the pressure pulse, just as under the control conditions; the peak of the volume pulse was reached early, but during the rest of the cycle its size relative to the pressure pulse remained constantly larger.

Discussion

Introduction of high-frequency currents into tissues as a means of measuring segmental blood flow is a widely used method today.[6,11] This method is based on the principle that at intermediate radio frequencies of the delivered current (around 100-1,000 kilocycles) most tissues are not stimulated, the interelectrode segment behaves like a pure resistance, and its reactive impedance factors approach zero. Thus, passive increase of the volume of the ininterelectrode segment will be directly related to the conductance between the electrodes, and conductance changes can thus be used as an indicator of local changes in volume. Choice of a somewhat lower oscillator frequency in the present unit (originally designed by Dr. Otto Schmitt, Minneapolis) was adopted for better penetration of interelectrode deep tissues, whereas higher frequency currents would tend to flow on the skin surface.

The described differences between pressure and impedance pulses of the examined arteries cannot be ascribed to phase lag of either one of the recording systems. Most of the described differences are of low basal frequency and occur in the relatively stable parts of each cycle. Relative lag or advance of features within both pulses frequently follow each other in the same cycle. On the other hand, the nature of the pulses is different; the arterial pressure pulse is a physical difference of pressures in a closed system, whereas the impedance pulse is a combination of arterial, capillary, and venous volume pulses between the two electrodes. By keeping the interelectrode distance at a minimum, one may reasonably assume that capillary and venous volume pulses are greatly reduced, whereas the arterial capacity changes are unaffected. Selective recording of changes in arterial volume can be assumed to have been obtained in the cases in which one electrode is the intra-arterial tip of a polyethylene catheter, and the other is the conducting tip of a short insulated needle positioned just outside the arterial wall at the level of the tip of the catheter. The upstrokes of all recorded impedance pulses must be due solely to changes in arterial capacity, which precede all capillary, etc., changes. In fact, if one uses two similar subcutaneous electrodes on either side of the artery, the recorded volume pulse is not different from that obtained between a subcutaneous and an intra-arterial electrode.

The differences between volume pulses obtained with the skin electrode and those obtained with the subcutaneous one (against the same intra-arterial electrode) must be ascribed to the large capillary volume of the interposed segment of skin; this would account for the larger over-all size, smoother contour, and slower diastolic decrease in pulses obtained with the skin electrode. Changes in contact resistance between skin and electrode due to movement, and reflected as impedance change, occur more easily with the subcutaneous electrode.

The use of a scalar system (subtraction) to record such vectorial relations as bidirectional relative changes of pressure and volume in time was imposed by reasons of necessity; we are aware of the shortcomings of this approach in expressing spatial relations. The main advantage of this method is that the finer details of pressure-volume relation have been made available to exact study in beat after beat, and this could not be done by observing the vectorial loop on a cathode-ray screen.

Our results agree in part with those obtained by Rushmer,[4] who used a rubber-mercury transducer to record changes in diameter of the aortic arch of dogs. Circumference increased earlier but also faster than did the pressure in this area; in his interpretation, Rushmer invokes the proximity of the left ventricle, which may pull as well as fill up the initial aortic segment; such longitudinal effects should be only secondary in the experiments reported herein. The faster increase of pressure (after a delayed start) in the present cases is probably due to the location studied. In fact, peripheral arterial pressure pulses have a significantly shorter "build-up" time, i.e., they rise faster than do central pulses.[8-10]

In a recent extensive article, Peterson and associates[5] have demonstrated by elegant and elaborate methods, involving computer analyses, a relative excess of volume over pressure pulse amplitude in canine arteries in situ during the major part of the downstroke. This is in accord with the present findings, and the authors attribute it to the viscous properties of the vessel wall; locally applied epinephrine accentuates this delayed volume response during diastole ("decreasing vascular stress"; cp. also herein Fig. 3, center). The two major differences between these data and ours are that (a) the upstroke differences reported herein are not obvious or referred to, and (b) the canine volume pulse contours lack the higher frequency oscillations described here. These differences may be due either to species differences or to the various differences in recording methodology employed. As a consequence, spectral analysis of Peterson's data indicates that amplitude of harmonics of any volume pulse drops to the background noise level beyond the fourth harmonic of the basic frequency. The data presented herein indicate the presence of sizable higher frequency components in

the human volume pulse, not present in the pressure pulse, and probably extending into the eighth harmonic of the basic frequency (Fig. 1, lower half; Fig. 3).

If the artery were a completely rigid tube, no change in volume would be recorded with each cycle but only change in pressure; actually, during each cycle the initial rise is that of volume,* but very rapidly (at about one tenth of the height of the volume pulse) the pressure also starts rising and overtakes the volume before its crest. The physical meaning of these relations cannot be determined with the present data, but it is interesting to note that during hypertension, in addition to decreased expansion, and accentuation of the delayed compliance of volume to pressure during the plateau and early diastole, there is a *faster* return to the base line of the volume pulse during late diastole (Fig. 3, center). This suggests that under the conditions of the present experiments the relationship of pressure and volume may not be linear, and that within *each cycle* periods of increased inertia (viscosity) and decreased inertia of the arterial wall may follow each other.

It should finally be noted that beat-to-beat variability of the volume pulses is marked in contrast to that of the pressure pulses. This variability is greatly reduced whenever segments of skin are involved between the electrodes, and is more marked with subcutaneous electrodes. If, as discussed, such variability of volume pulse reflects changing uptake capacity of arteries, determination of cardiac output by the pulse contour method will be subject to errors, related to this varying capacity. Such a possibility is more likely in peripheral, muscular arteries.

In conclusion, the described pressure-volume relations of the brachial and femoral arteries of the young male are consistent with their nature as visco-elastic tubes. During short periods of hypertension these arteries become stiffer, inertial properties are exaggerated, and nonlinear elastic properties seem to appear; during amyl-nitrite hypotension, normal relations are accentuated. These changes indicate active participation of elements within the arterial wall in usual vasomotor reactions, in addition to the changes of the terminal vascular bed.

*During extrasystoles occurring after a very short pause, volume pulses have been recorded unaccompanied by pressure pulses.

Summary

1. Pressure pulses and volume pulses were obtained simultaneously and from the same site of the brachial or femoral artery in 13 young men. Pressure pulses were obtained through a Cournand needle or a short PE-90 catheter connected to a Statham P23AA gauge and DC-amplifier. Volume pulses were obtained by recording impedance changes between the Cournand needle or the tip of the catheter and a cutaneous lead disc placed over the tip of, or a subcutaneous needle (insulated except its tip) inserted as near as possible to the tip of, the Cournand needle or the catheter. The intra-arterial and extra-arterial needles were used for both introducing current and recording resistivity changes.

2. Recorded pressure and volume pulses were compared by adjusting the size of the latter to equal exactly that of the former. Pressure pulses were then fed as positive, and volume pulses as negative, input to a subtracting DC-amplifier. The subtraction curve, as well as the original pulses, were simultaneously recorded.

3. The foot of the volume pulse preceded that of the pressure pulse by a mean of 0.010 second at the elbow. Thereafter, the rise in volume exceeded only briefly the rise in pressure. Thus, the peak was reached first for the pressure and then for the volume pulse. The mean time at which equal heights of upstroke were reached was 0.035 second. The dicrotic notch occurred later in the volume pulse, so that the over-all duration of volume systole exceeded by 0.04 to 0.06 second that of the pressure systole.

4. In diastole the height of the volume pulse decreased more slowly than did that of the pressure pulse. The over-all area of the volume pulse exceeded the comparable area of the pressure pulse, despite equal maximal heights; the mean ratio of these areas in the 13 young men was 127:100. No major differences were observed between volume pulses recorded with a skin electrode and those recorded with a sub-

cutaneous electrode, apart from "stabler" pulses obtained with the former electrode.

5. Momentary hypertension was associated with volume pulses diminished in size; their systolic phase lasted still longer, but in diastole the return to the base line was faster. The delay in onset of the pressure pulse got shorter, and, on occasion, the rise in pressure preceded the rise in volume; amyl nitrite reversed these trends.

6. These data indicate that the brachial artery in the young is a partly distensible elastic tube, whose wall becomes, as a whole, more rigid and inert during hypertension, and more distensible during amyl-nitrite hypotension. Nonlinear relations of pressure and volume in parts of the cycle, particularly in hypertension are suggested. Beat-to-beat arterial capacity seems variable, and this justifies skepticism in regard to determinations of cardiac output with the pressure pulse contour method.

7. Intravascular impedance plethysmography in association with simultaneous manometric data can give significant information on the properties of the vessel under study.

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The application of boundary potentials to several electrocardiographic problems

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It is the purpose of this communication to briefly outline a particularization of the Gabor-Nelson equations[1] for the circular lamina, with the purpose of determining the minimal number of electrodes which may be required to yield accurate dipole location.

In addition, a *short method* will be described by which dipole location may be determined accurately from the measurement of four boundary potentials.

In previous communications[2,3] it has been pointed our that the Wagner-Ground reference potential of Frank and Kay[4] is not, as they contend, equivalent to their arbitrary choice of zero potential at infinity. In these communications[2,3] it was stated that the Wagner-Ground potential is, in fact, a function of dipole position and of dipole axis direction. It is the purpose of this communication to describe the Wagner-Ground potential in mathematical terms with reference to the circular homogeneous lamina. In a previous communication[5] the "grid-lead" central terminal was described for use as a reference potential equivalent to that of zero potential at infinity. It is the purpose of this communication to support this argument with further expansions of dipole potential theory, with multipole potential theory, and with experimentations in which the net pole strength of the multipole is zero.

Method 1

The Gabor-Nelson equations for finding the dipole moment from a summation of the potentials on the boundary are[6]

$$(1) \qquad \begin{cases} M_x = \dfrac{Rd}{\rho} \oint V_s \cos \Phi d\Phi \\ M_y = \dfrac{Rd}{\rho} \oint V_s \sin \Phi d\Phi \end{cases}$$

when particularized for the circular lamina. Here, M_x is the moment of the dipole parallel to the axis of X; M_y is the moment of the dipole parallel to the axis of Y; R (=24.9 cm.) is the radius of the circular lamina; d (=1.94 cm.) is the depth of the conducting fluid measured in centimeters; ρ is the specific resistance of the fluid in ohm centimeters; V_s is the "unipolar" or "bipolar" potential at any boundary electrode or between one and all the other electrodes on the boundary; and, finally, Φ is the angle made by the positive axis of X and the radius vector to the boundary electrode at which V_s is measured.

In our experience, the most suitable way to determine the value of ρ is to measure the boundary potential V_s for the centric dipole where $\Phi = 0$, that is, on the positive axis of X. Here, $V_s = 2M/R$, and in the current experiments, $V_s = 30$ mv. (P-P). Now, M is known to be equal to 373.5 Ma.-cm. (P-P). We also have $M = ID\rho/2\pi d$.[7]

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$$(2) \qquad V_s = \frac{2M\Psi_x}{R}\left\{\frac{\lambda - f\lambda_1}{1 + f^2 - 2f\gamma}\right\} + \frac{2M\Psi_y}{R}\left\{\frac{\mu - f\mu_1}{1 + f^2 - 2f\gamma}\right\}$$

$$(3) \qquad \begin{cases} \bar{X}M_x - \bar{Y}M_y = \dfrac{R^2 d}{\rho} \oint V_s \cos(2\Phi)\, d\Phi \\ \bar{X}M_y + \bar{Y}M_x = \dfrac{R^2 d}{\rho} \oint V_s \sin(2\Phi)\, d\Phi \end{cases}$$

$$(4) \qquad \begin{cases} V_{s,x} = \dfrac{2M}{R}\left\{\dfrac{\lambda - f\lambda_1}{1 + f^2 - 2f\gamma}\right\} = \dfrac{2M(x-h)}{(x-h)^2 + (y-k)^2} \\ V_{s,y} = \dfrac{2M}{R}\left\{\dfrac{\mu - f\mu_1}{1 + f^2 - 2f\gamma}\right\} = \dfrac{2M(y-k)}{(x-h)^2 + (y-k)^2} \end{cases}$$

If D (=2.5 cm.) is the distance between the poles of the dipole electrode, and I(=5.3002 Ma.) (P-P) is the current through the dipole electrode (determined by experimental measurement), we get $\rho = 336$ ohm cm. for the specific resistance of tap water at the Oklahoma Medical Center. With these results, it is clear that $Rd/\rho = 0.1406$ for the constant in Equation 1. There are two ways to obtain the value of V_s at any given number of points on the boundary of the circular lamina. They can be computed from the Equation 2 (*top of page*)[7] or the value of V_s can be measured with reference to the potential V_T (=0) of an averaging network.[2] In the following experiments, V_s was computed by Equation 2 through four significant digits. The arbitrary dipole midpoint was chosen 3 cm. along the positive axis of X and 10 cm. along the negative axis of Y. The dipole axis was taken at 45 degrees from the positive X-axis (Fig. 1). This rather laborious computation was done in order to remove errors which are introduced by the model or in reading the detector circuit.[2] In Equation 2, Ψ_x is the cosine of the angle made by the dipole axis and the positive axis of X; Ψ_y is the cosine of the angle made by the dipole axis and the positive axis of Y;λ and μ are the direction cosines of the angle between the X and Y axes and the radius vector R from O, the center of the circular lamina, to the point on the boundary at which V_s is measured; λ_1 and μ_1 are the direction cosines of the angles between the positive X and Y axes, respectively, and radius vector from O to the dipole midpoint; and, finally, γ is the cosine of the angle θ between the radius vector to any boundary electrode of potential V_s and the radius vector from O to the dipole midpoint (Fig. 1). Here, $\gamma = \lambda\lambda_1 + \mu\mu_1$.[7] Also, in Equation 1, $d\Phi$ is the increment of arc along the circumference of the circular boundary, and, if V_s is taken at every 5 degrees of arc, $d\Phi = 5\pi/180° = 0.0873$. If V_s is taken at every 10 degrees of arc, $d\Phi = 10\pi/180° = 0.1745$, etc.

Table I shows that using 9 or more, but not fewer, electrodes gives satisfactory values of the first order moments M_x and M_y of the potential.

The Gabor-Nelson equations for the *second* order moments $\bar{X}$, $\bar{Y}$ of the boundary potentials as particularized for the circular lamina are as in Equation 3 (*top of page*),[6] wherein $\bar{X}$ and $\bar{Y}$ are the coordinates in centimeters of the dipole midpoint position. All remaining symbols have been defined under Equation 1 and in the footnote to Table IIB. Examination of the two right-hand columns in Table I shows that 9 or more, but not fewer, boundary electrodes at equal arc lengths are sufficient for accurate dipole midpoint location.

Method 2

If we denote by $V_{s,x}$ the boundary potential when the dipole axis is parallel to the X-axis, and by $V_{s,y}$ the boundary

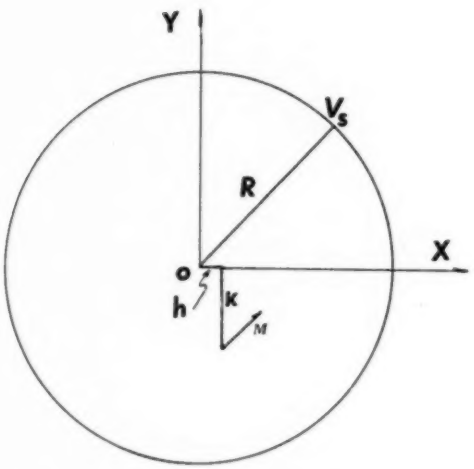

Fig. *1*. Circular lamina of radius *R* with dipole midpoint location at the origin of the vector moment *M* at (*h*, *k*) from the center *0*. V_s is any boundary potential. The vector $\overrightarrow{fR}$ from 0 to the origin of *M* is not shown. The magnitude $fR = \sqrt{h^2 + k^2}$. In the computations, h = 3 and k = −10 (Table I). For this particular dipole location, the Wagner-Ground reference of Frank and Kay introduces a 44.2 per cent error in the origin of the rectangular coordinates on the "image" map. The *unipolar potentials* and the potential differences between the boundary electrodes and the Wagner-Ground ($V_s - V_w$) all lie on the image circle of radius $R' = 36.40$ mv. (P-P). Here, $R' = 2M/R(1\text{-}f^2)$ (P. M. Berry).

potential when the dipole axis is parallel to the Y-axis, Equation 2 takes on the form of Equation 4 (*top of page 685*). We now have

$$(5) \quad N \equiv V_{s,y}/V_{s,x} = (y - k)/(x - h).$$

For the particular boundary electrode on the positive axis of X, $y_1 = 0$, and $x_1 = R$. Equation 5 now gives $N_1 = k/(h\text{-}R)$. For the particular boundary electrode on the negative axis of Y, $x_2 = 0$, and $y_2 = -R$. Equation 5 now gives $N_2 = (R + k)/h$. We then have

$$(6) \quad h = \frac{R\,(1 - N_1)}{N_2 - N_1},\ k = \frac{RN_1\,(1 - N_2)}{N_2 - N_1}$$

where h and k are respectively the $\overline{X}$ and $\overline{Y}$ coordinates of the dipole midpoint. This result is obvious by inspection of Equation 5, where R ($= \sqrt{x^2 + y^2}$) is the radius of the circular lamina, the center of which is located at (h, k) from the dipole midpoint position. By means of a precision mechanical stage for locating and relocating the dipole electrode (Fig. 2) and the detector circuit described elsewhere,[2] values of h and k may be determined to within 0.15 per cent accuracy. When h and k are solved, these values may replace their identities in the right-hand side of Equation 4 for a solution of the dipole moment M (Equation 2).

Method 3

It has been reported by this laboratory that V_w, the potential of the Wagner-Ground, is a function of both dipole location and dipole axis direction.[2,3] Insofar as the circular lamina is concerned, repeated experiments confirm this contention and show, in fact, that

$$(7) \quad V_w = \frac{\pi Rd}{\rho}\left(\frac{V_s + V_s'}{2}\right)\cos\alpha$$

or, if the formulae for V_s and V_s' are replaced in Equation 7 by their identities from Equation 2, the result is

$$(8) \quad V_w = \frac{ID}{2}\left(\frac{2f}{1 - f^2}\right)\cos\alpha.$$

In Equation 7, V_s and V_s' are the two measured boundary potentials at the poles of a diameter of the circular lamina taken through the radius vector $\overrightarrow{fR}$ drawn from the center of the circular lamina to the dipole midpoint, with the dipole axis along the diameter specified. In using Equation 7, V_s and V_s' are measured directly in millivolts (P-P). Also, α is the angle made by the positive axis of the dipole and $\overrightarrow{fR}$. R is the radius, in centimeters, of the circular lamina; d is the depth, in centimeters, of the fluid conductor (tap water); and ρ is the specific resistivity, in ohm centimeters, of the conducting fluid. In Equation 8, I is the R.M.S. current through the dipole electrode, and D is the distance, in centimeters, between the outer surfaces of the dipole electrode. If ID is determined in R.M.S. value, then ID/2 in Equation 8 holds. For comparable values determined by Equation 7, where V_s and V_s' were measured in peak-to-peak values, ID/2 is multiplied by $2\sqrt{2}$, and the constant in Equation 8 becomes $ID\sqrt{2}$. The central terminal of potential V_T from 72 boundary electrodes has been shown to have a zero of potential equivalent to zero potential

at infinity,[3,8,9] and, moreover, V_T is independent of dipole location or dipole axis direction. We can thus measure V_w, the Wagner-Ground potential, directly, using the lead,

$$(V_w - V_T) = V_w. \tag{9}$$

Consequently, Equations 7, 8, and 9 offer three methods for a determination of V_w. Table IIA gives the results of all three methods, using 17 values for fR, the magnitude of the dipole eccentricity. During these experiments the dipole axis was arbitrarily kept in the direction of the positive X-axis, which, in turn, was chosen along the line of eccentric positions. Consequently, when the eccentricity was along the positive X-axis, cos α (= +1) gave positive values for V_w, but when equal eccentricities were taken along the negative X-axis, cos α (= −1) gave negative values for V_w (Table IIA). Moreover, rotations of the dipole axis at all eccentricities precisely described the proportional function cos α of Equations 7 and 8.

Method 4

The Nelson formula[10] for the potentials on the boundary of an ellipse was programmed on the 650 IBM computer for boundary potentials at equal central angles of every 5 degrees.[3] This program was changed to compute the potentials at 72 *equal lengths* of *arc* around the boundary of the ellipse. Three ellipses of markedly different shape were used, together with two different dipole positions in each ellipse. In all six instances the sum of the 72 bound-

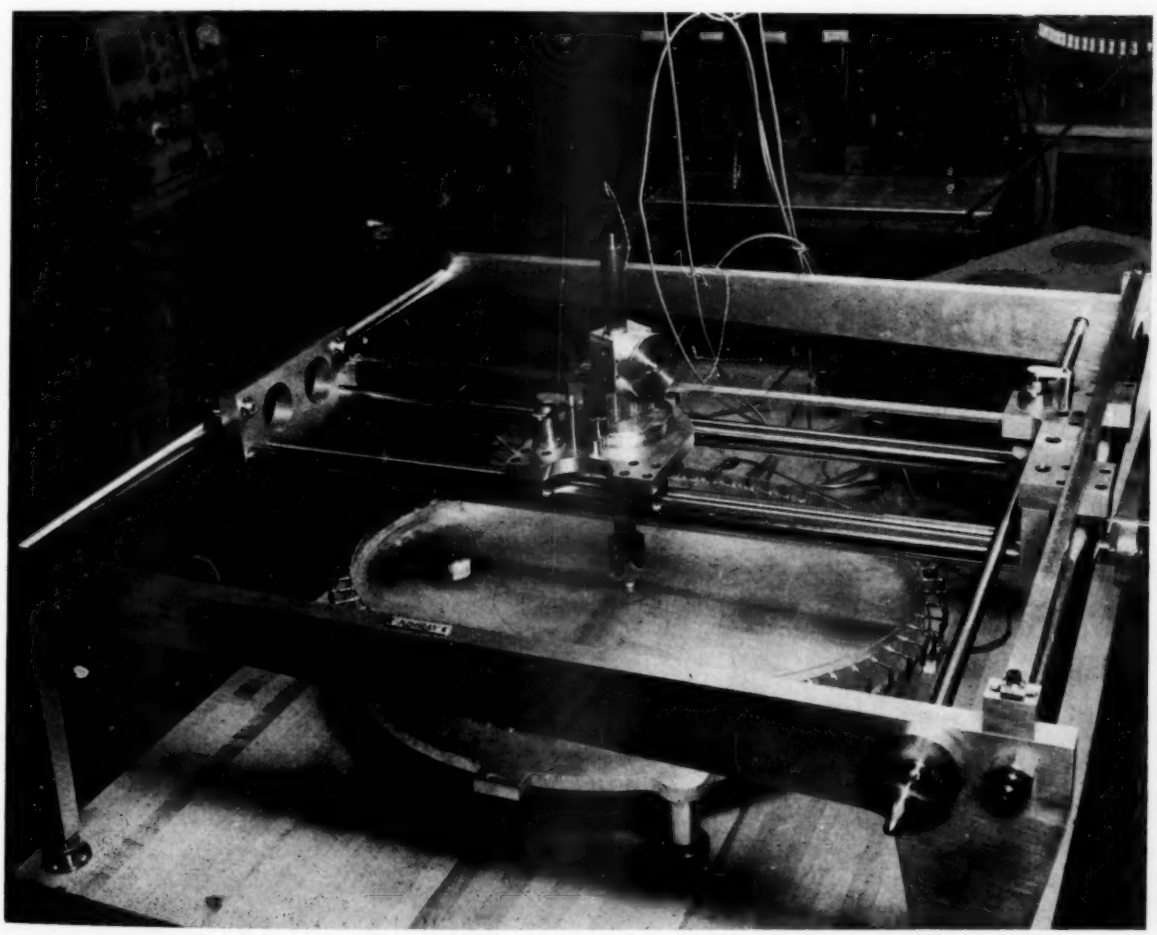

Fig. 2. Precision mechanical stage with four dimensions of freedom, motion along X, along Y, and along Z. The electrode stage proper permits accurate degrees of rotation of dipole axis. Positioning of the dipole midpoint is accurate to within 0.002 cm. Dipole electrode is depicted at the center of the elliptical lamina. All resistors (72) are equal, with a tolerance of 1 per cent and may be seen connecting the boundary electrodes to the averaging buss of potential V_T. The electrodes are spaced at equal arc lengths along the boundary of the ellipse.

Table I. *Dipole moments and dipole midpoint coordinates computed with the Gabor-Nelson formulae for the circular lamina*

n	*Equation 1*		*Equation 3*	
	M_x (*P-P*)	M_y (*P-P*)	$\overline{X}$ (*cm.*)	$\overline{Y}$ (*cm.*)
72	9.378	9.379	3.00	−10.00
36	9.369	9.371	2.99	−10.00
24	9.397	9.406	3.02	−10.03
18	9.366	9.373	2.99	−9.99
12	9.371	9.367	2.99	−10.00
9	9.358	9.403	3.08	−9.99
9′	——	——	2.98	−9.99
Correct values	9.366	9.366	3.00	−10.00

n is the number of boundary electrodes. Under M_x and M_y are the dipole moments computed from Equations 1 and 2. Under $\overline{X}$ and $\overline{Y}$ are the coordinates, respectively, of the dipole midpoint position. They are given in centimeters and were computed using Equation 3. These values are *independent* of the *constants* used in computing M_x and M_y, but depend upon the ratio M_y/M_x. When n is 6, values for M_x and M_y are unsatisfactory.

ary potentials was zero. This result indicates that, if V_s is the potential defined by the Nelson equation,[10] we must have

$$\overline{V} = \oint V_s \, ds = 0 \tag{10}$$

for any dipole location in an ellipse of any shape. In Equation 10, $\overline{V}_s$ is the average value of the boundary potentials V_s, and ds is an element of arc. If ds is an element of surface and $\oint_s$ indicates a surface integral, Equation 10 holds for any body of nonre-entry form.

To confirm Equation 10 experimentally, 72 electrodes spaced at equal arc lengths along the boundary of the ellipse a/b = 1.32 were connected to a central terminal through *equal* resistances (Fig. 2). The potentials ($V_s - V_T$) were then measured using an arbitrary dipole position, and these potentials were compared with the unipolar potentials computed by the 650 IBM computer programmed on the C. V. Nelson formula.[10] The experimental results were highly satisfactory. Thus, Equation 10 is confirmed by both computer and laboratory experimentation.

Equations of the types 1 and 3 were particularized for dipole location in the ellipse of arbitrary shape and programmed for the 650 IBM computer. Table III shows the computed dipole locations which resulted from two sets of potential measurements using the generator and detector circuit described elsewhere.[2] These potentials are comparable in accuracy to those which can be measured with modern photographic electrocardiographic equipment.

Discussion

The Gabor-Nelson equations[1] when particularized for the circular and the elliptical lamina result in accurate dipole midpoint location when more, but not fewer, than 9 boundary potentials or potential differences enter these summations. Inasmuch as these equations are completely general for a nonre-entry form of three- and two-dimensional shapes when locating a dipole (or a multipole of higher order) by the arbitrary measurement of boundary potentials or potential differences, these equations must be regarded as the most important mathematical contribution to electrocardiography since that of Helmholtz[11] in 1853.

The "short method" of dipole midpoint location in the circular lamina is equally accurate when used with a precision mechanical stage for the dipole electrode (Fig. 2). These simple equations (4, 5) may be equally useful when using a turtle heart beating in a circular lamina, or in studying an arbitrary multipole (of zero net pole strength) located centrically or eccentrically in the circular lamina.

When unipolar potentials are used with a beating heart, it will be necessary to in-

Table IIA. *The values of the Wagner-Ground potential* V_w *as determined by Equations 7, 8, and 9 for various values of eccentricity fR*

fR (cm.)	*Equation 7* V_w *(mv.)*	*Equation 8* V_w *(mv.)*	*Equation 9* V_w *(mv.)*	*Sphere factor*
0	0	0	0	
±2.54	±1.32	±1.36	±1.50	2.52
±5.08	±2.87	±2.82	±2.95	2.59
±7.62	±4.56	±4.47	±4.50	2.71
±10.16	±6.51	±6.48	±6.25	2.90
±12.70	±9.27	±9.12	±9.00	3.20
±15.24	±12.81	±12.96	±13.00	3.70
±17.78	±19.21	±19.30	±19.20	4.58
±20.32	±31.80	±32.36	±33.50	6.49

The experimental values were I = 1.8742 Ma. (R. M. S.) D = 2.5; ID $\sqrt{2}$ = 6.6253; d = 1.94 cm.; R = 24.9 cm.; ρ = 336; and $\pi Rd/\rho$ = 0.4417. The measured values of $(V_s + V_s')/2$ are shown in Table IIB along with the computed values of $2f/(1 - f^2)$. According to Equation 7 the value of $(V_s + V_s')$ is multiplied by 0.4417, and the value $2f/(1 - f^2)$ of Equation 8 is multiplied by 6.6253. All values for V_w are given in millivolts peak-to-peak. At each value of the eccentricity the dipole was rotated through 60 and through 90 degrees. In the first instance, the value of V_w changed to one half of the value shown under V_w of Equation 9. In the second instance, V_w vanished. These and other degrees of rotation at all 16 values of fR established that V_w was proportional to cos α as described in Equations 7 and 8. Column five under "sphere factor" indicates the number of times the Wagner-Ground potential V_w would be increased when used with a spherical conductor. For example, at fR = 12.70 cm., about half the radius, V_w is at 9.12 millivolts in the circular dish. In the spherical conductor this value is increased by 3.20 times.

troduce four simultaneous potentials in order to eliminate the unknowns Ψ_x and Ψ_y in a solution of h and k. Similar transformations apply to a three-dimensional homogeneous media.[12]

Under Method 3 are described three different approaches to a solution of the Wagner-Ground reference potential of Frank and Kay.[4] The three methods yield essentially identical results and may be regarded as a conclusive demonstration of the nonunipolar Wagner-Ground error. The absolute magnitude of this error is not widely appreciated. In the current study, the average magnitude of 72 values for V_s (without regard to sign) was 20.23 mv. (P-P), with a maximum of −43.90 mv. (P-P) on electrode Φ = 255°, and a minimum of −0.41 mv. (P-P) on electrode Φ = 145°. Consequently, Table IIA indicates that for all values of fR other than zero the Wagner-Ground error is such as to make this reference unacceptable for the direct measurement of *unipolar* potentials.

It has been suggested by Gaselowitz[13] that the Wagner-Ground error of Equation 9 would be minimized by having the poles of the dipole electrode smaller and separated by a smaller distance D of Equation 8. The results on V_w in column three of Table IIA are computed by the dipole Equation 8, where the separation of point-poles is infinitesimal and their agreement with the data of columns two and four does not appear to support these contentions. Gaselowitz has also reported[13] that the Wagner-Ground error "might be minimized in using a three, rather than a two, dimensional conductor." Examination of column five of Table IIA together with column three of Table IIB shows that the Wagner-Ground error V_w is increased rather than decreased in passing from a circular dish to a sphere. One has only to multiply the potentials in column three of Table IIA by the numbers in column five of that table

Table IIB. *Measured and computed values for determining* V_w *by Equations 7 and 8, respectively*

fR (cm.)	$\frac{V_s + V_s'}{2}$ *(mv.)*	$\frac{2f}{1 - f^2}$ *(circle)*	$\frac{5 - f^2}{2(1 - f^2)}$ *(sphere)*
0	0	0	
±2.54	3.00	0.2061	2.521
±5.08	6.50	0.4252	2.587
±7.62	10.30	0.6752	2.707
±10.16	14.75	0.9789	2.899
±12.70	21.00	1.3786	3.203
±15.24	29.00	1.9569	3.698
±17.78	43.50	2.9131	4.581
±20.32	72.00	4.8842	6.488

The values under $(V_s + V_s')/2$ were measured, and the values under $2f/(1-f^2)$ were computed. The quantity $(5-f^2)/2(1-f^2)$ when multiplied by $2f/(1-f^2)$ gives (except for the constant) $1/2\ (V_s + V_s')$ for the sphere. Here again, V_s and V_s' are defined as the boundary potentials at the poles of a diameter taken through the radius vector $\overrightarrow{fR}$ drawn from the center of the sphere to the dipole midpoint. The dipole axis for these potentials is along the diameter specified. When it is not so directed, the function cos α takes care of both the sign and magnitude of V_w. In order to obtain these results, all shielding is connected to the Wagner-Ground. This includes both shields of the isolation transformer which couples the oscillator (generator) with the dipole electrode.

Table III. *Dipole midpoint coordinates computed by the 650 IBM computer, using the Gabor-Nelson equations for the elliptic lamina*

n	$\overline{X}$ (*cm.*)	$\overline{Y}$ (*cm.*)
72	−4.96	−7.58
36	−4.88	−7.59
24	−4.96	−7.63
18	−4.93	−7.57
12	−5.02	−7.58
Correct values	−5.08	−7.62

The dipole potential differences between electrode $\Phi = 0°$ and al other 72 electrodes located at equal arc length on the boundary of an elliptical lamina were measured for each of two dipole axis directions 70 degrees apart. These potentials were then carded into the 650 IBM computer program for calculation of the dipole midpoint coordinates. The results are shown in the table. Note that the 24 potentials from 12 electrodes (at equal arc lengths) give dipole midpoint location as accurate as the 144 potentials from 72 electrodes. These potential differences were measured with slightly better accuracy than those which might be obtained from the human high-speed photographic electrocardiogram. Dipole-locating stage and conducting lamina are shown in Fig. 2. The dipole moment components M_x and M_y are not determined separatetly since they enter the computer formulae only as a proportional factor, and the constants d/ρ (depth and specific resistivity) divide out of the equations. (Computer work was carried out by P. M. Berry, B.S., at the Computer Laboratory, University of Oklahoma, Norman, Okla.)

to obtain the Wagner-Ground unipolar error for the sphere.

Examination of Equations 7, 8, and 9, together with Tables IIA and IIB, makes clear the nature and magnitude of the Wagner-Ground error V_w. With reference to the *dipole generator network*, V_w is a *kind* of "dipole midpoint" potential. With reference to the zero of potential at infinity,[2,3,8,9] V_T of Equation 9 agrees precisely with the zero of potential adopted in the *mathematical* theory of Frank and Kay.[4] If V_w is used according to the method proposed by Frank and Kay, the dipole must be confined to the *centric position* in the circular lamina or in the sphere where $f = 0$, or the medium must be made infinite. V_w can be used as a reference potential for unipolar potential measurements with eccentric dipole positions in plane or in volume conductors of finite extent when, and only when, its *explicit potential function* is *known*. The value of the potential function can then be subtracted from the potential difference measured for obtaining the unipolar value. The V_w function is changed when the boundary contour is changed, and we have not as yet solved this function for the ellipse. In transfer of the dipole electrode to the torso model from the sphere or hemisphere, Frank and Kay introduced an unknown potential function for V_w which vanished upon return to centric position of the simple model. In the simple conductors studied in this laboratory, V_w is shown to be a function of certain *boundary potentials* when compared to the arbitrary zero of potential at infinity, or when compared with any potential that differs from this zero by, at most, a constant while the location of the dipole midpoint and the direction of the dipole axis are allowed to vary. V_w has the added disadvantage of being thermolabial and chemolabial across the contact surfaces of the dipole electrode.

Equation 10 appears to hold for a plane or volume conductor of any nonre-entrant shape, and V_s may be regarded as the potential at any boundary point due to any multipole of zero net pole strength. This generalization is supported further by the residue-theorem for the complex variable.[14] Electrodes which are equally spaced on a broad elastic belt that stretches onto the chest at the heart level results in an electrode spacing at *equal arc lengths*. This system of electrodes[5] can then be connected to a common terminal through *equal* resistances. This terminal has then a potential equivalent to the customary choice of zero potential at infinity.[3,8,9] A belt of similar construction, using 9 or more electrodes, can be utilized for dipole location provided 18 or more potentials are entered into the summations of the Gabor-Nelson equations (Table I).

Summary

1. The Gabor-Nelson equations require a minimal of 18 or more boundary potentials or potential differences for computation of dipole midpoint location in the insulated two-dimensional conductor. The 18 or 24 potentials are best taken from 9 or 12 electrodes, respectively, using two dipole axis directions.

2. The Wagner-Ground reference potential of Frank and Kay is shown to be a function of certain *boundary potentials*. This function *changes* when the *boundary*

contour is *changed*. Its explicit formula is presented for the circular lamina and for the sphere.

3. The equation for central terminal of zero potential using equal resistances is presented for an ellipse of any shape. Its validity is supported by computer experiments and by laboratory investigation.

4. Experimental and computer data indicate that highly accurate dipole location may be obtained in the circular or in the arbitrary elliptical lamina using 18 potentials from as few as 9 boundary electrodes.

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Case report

Paroxysmal ventricular tachycardia associated with myxedema A case report

James E. Hansen, Major, MC, USA
Denver, Colo.

Ventricular tachycardia rarely occurs in the absence of serious heart disease, especially in a patient over 40 years of age. In the case reported the usual etiologies of paroxysmal ventricular tachycardia were not found, and simultaneously occurring myxedema was believed to be the cause.

Case report

A 42-year-old housewife was admitted to an army hospital on March 29, 1959, because of ventricular tachycardia. The patient had enjoyed excellent health until the summer of 1958, when fatigability and menometrorrhagia began. Administration of ferrous sulfate resulted in a rise in her hemoglobin from 9.5 to 12.0 Gm.

Uterine dilatation and curettage in December, 1958, showed late secretory phase endometrium. A chest x-ray film at this time showed in the right lower lung field a partially calcified density which had enlarged since examination a year before. Intradermal coccidioidin and histoplasmin tests were positive; the second strength tuberculin test was negative. A large granuloma was removed from the right lower lobe on Jan. 16, 1959. No specific etiology was established by microscopic or cultural examination. Convalescence was slow.

After discharge from the hospital on Feb. 4, 1959, she became so exhausted that she could not return to her normal activities. She noted increasing weakness, clumsiness and puffiness of the hands, and puffiness of the face, especially about the eyes. Although she was a talented musician, she lost her ability to sing. She was aware of thinning of the axillary and scalp hair, but unaware of any mental retardation or definite cold intolerance.

On March 27, 1959, she developed a cough, sore throat, and coryza, which cleared by the following evening. After breakfast on March 29, she suddenly noted light-headedness and darkening of the vision, followed by an oppressive, tight, substernal discomfort and feeling of suffocation. A few moments later she was aware of her heart pounding. The chest discomfort was replaced by a burning sensation of the forearms. The pounding ended abruptly, less than 10 minutes after onset. The patient estimated that 12 to 15 similar episodes occurred during the day, each lasting from 3 to 10 minutes and accompanied by chest pain of less than 5 minutes' duration. The patient had never before experienced palpitation, light-headedness, shortness of breath, or arm or chest pain or pressure. She did not smoke and had not been emotionally upset. There was no family history of endocrine or heart disease. Her mother, an asthmatic, died at age 49. Her father, 11 siblings, husband, and three children were all in apparent good health.

The patient was seen in the emergency room, where an electrocardiogram showed multifocal premature ventricular contractions and abnormal T waves (*1830, March 29*, Fig. 1). While being observed there, she suddenly felt faint. The pulse was then found to be 190, and the blood pressure was 80/70 mm. Hg. Carotid massage, eyeball pressure, and tongue pulling had no effect. The electrocardiogram at that time showed ventricular tachycardia (*2200, March 29*, Fig. 1). The tachycardia lasted approximately 30 minutes, and stopped spontaneously while she was enroute to the ward.

Further examination revealed a sallow-complexioned, gray-haired, cooperative, psychomotor-retarded, and apprehensive Caucasian female. Her height was 67 inches, weight 128 pounds, temperature 98.6°F., pulse 80, and blood pressure 90/72 mm. Hg. The scalp hair was sparse, coarse, and dry. Facial edema was evident in retrospect. The pharynx was slightly reddened, but there was no exudate or adenopathy. The thyroid was not palpable. The heart tones were of poor quality. No

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murmurs were heard. There was no evidence of congestive failure. Deep tendon reflexes were present, but there was marked pseudomyotonia and weakness of the skeletal muscles. There was no abnormal pigmentation in the surgical scars. The palms of the hands and soles of the feet were conspicuously yellow.

The chest x-ray film revealed scattered pulmonary calcifications. The heart size and shape were normal. The leukocyte count was 13,200, with 80 per cent neutrophils, 15 per cent lymphocytes, 4 per cent monocytes, and 1 per cent eosinophils. The hemoglobin was 13.5 Gm. per cent, hematocrit 37 per cent, erythrocyte count 3,870,000, platelet count 220,000, sedimentation rate (Wintrobe) 40 mm. uncorrected, glutamic oxalacetic transaminase 22 units, glutamic pyruvic transaminase 7 units, protein-bound iodine 1.9 micrograms per cent, and serum cholesterol 309 mg. per cent. The heterophil antibody titer was

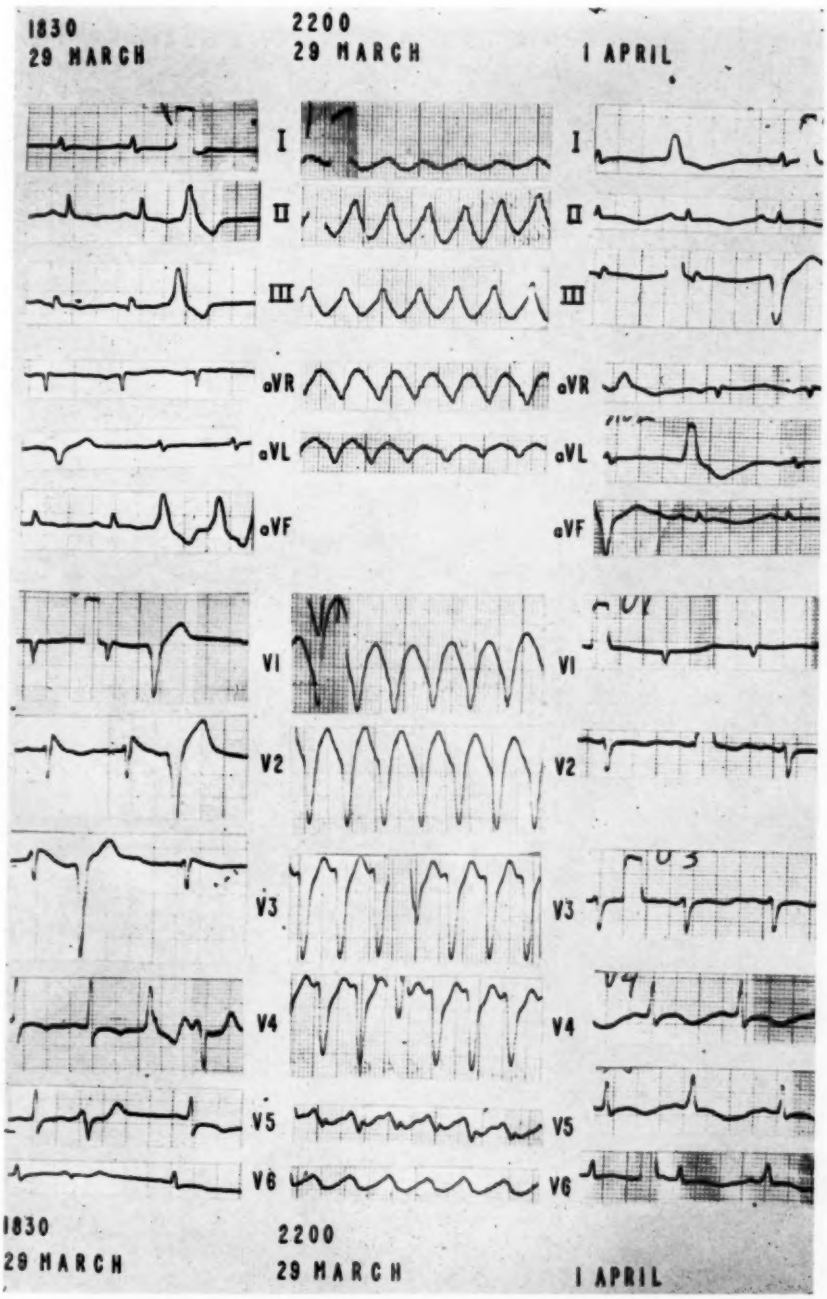

Fig. *1.* Electrocardiograms recorded on day of admission and 3 days later. Frequent ventricular premature contractions are seen in left and right tracings. Middle tracing shows ventricular tachycardia; no definite P waves are seen. Note similarity of premature ventricular contraction complexes in first tracing to those of the paroxysm.

1:112; differential absorption was not done. The basal metabolic rate was −32. The urinalysis, cardiolipin, serum protein, calcium, and phosphorus, and two throat cultures were normal.

The patient was maintained initially on small quantities of phenobarbital and 1.2 to 1.6 Gm. of quinidine sulfate daily. She had no further chest pain nor recognized episodes of tachycardia. She remained afebrile, without evidence of congestive failure. Urine output was adequate. The blood pressure stabilized in the range of 97-72/70-60 mm. Hg. The heart tones remained poor. There were no murmurs, but occasionally a dull or leathery third heart sound was heard. Serial electrocardiograms showed further lowering of the QRS amplitude, nonspecific T-wave abnormalities, prolongation of the Q-T interval, and premature ventricular contractions (Figs. 1 and 2). There was no evidence of myocardial infarction. Daily leukocyte counts and blood smears were normal. No atypical lymphocytes were seen.

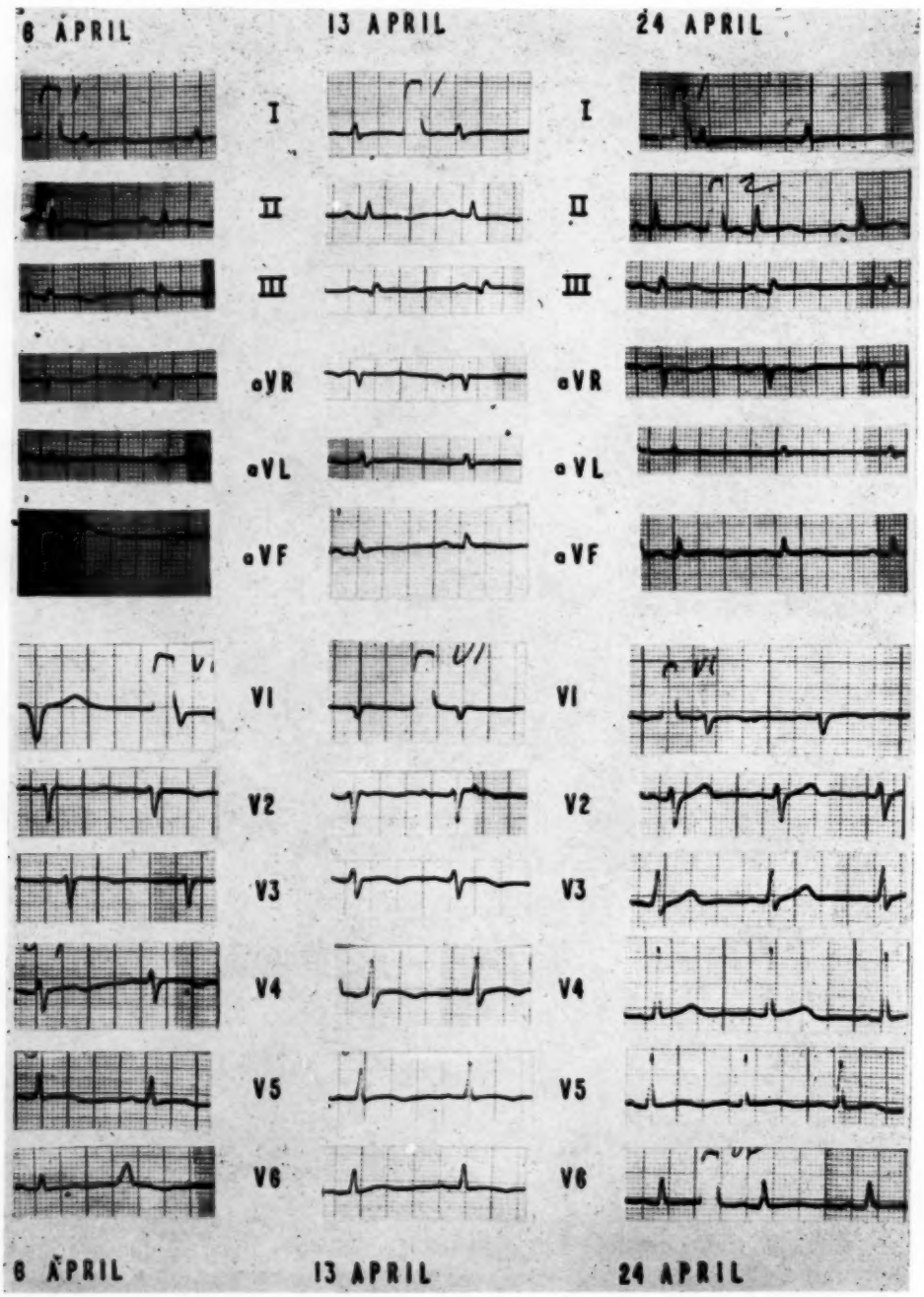

Fig. 2. Electrocardiograms recorded on day prior to institution of thyroid therapy and after 6 and 19 days of thyroid therapy. Note gradual but definite increase in voltage of QRS complexes, change from inverted to normal T waves, and cessation of ventricular premature contractions.

Serum transaminase (SGOT and SPT) determinations of March 30 and 31 and April 1, 2, 3, and 6 were normal. Chest x-ray films taken on April 6, with the patient in the upright and supine positions, were unchanged.

Fifteen milligrams of thyroid extract daily was started on April 7. The daily dosage was gradually increased to 120 mg. by April 17. Full ambulation was allowed by April 13. No premature ventricular contractions were noted on frequent electrocardiograms after April 13, except for two such contractions on April 22. The electrocardiogram showed marked improvement by April 24 (Fig. 2) and became normal May 1. The patient's blood pressure rose to the range of 108-100/80-70 mm. Hg. The basal metabolic rate rose to −9. The patient was discharged from the hospital April 24, feeling warmer, stronger, and less clumsy. The protein-bound iodine was 4.1 μg per cent, and the serum cholesterol was 191 mg. per cent on May 1, 1959. By late May, 1959, the patient had lost 9 pounds and was strikingly improved in appearance, intellect, strength, and coordination. Normal menses returned. She has been maintained on 120 mg. of thyroid extract daily. In December, 1960, she felt well and had a normal electrocardiogram, hemogram, and blood chemistries.

Discussion

Although the patient's history is complicated by the removal of the granuloma of the right lower lobe of the lung, her hypothyroidism apparently began in mid-1958. Her symptomatology, laboratory data, and striking response to the administration of thyroid extract made the diagnosis of myxedema certain. An additional endocrinopathy, such as hypopituitarism, was most unlikely, because of her lack of amenorrhea and her satisfactory response to thyroid alone.

Paroxysmal ventricular tachycardia is difficult to diagnose with certainty, even with the electrocardiogram.[1] Despite the fact that separate P waves could not be identified during the paroxysm, the tracing of *2200, March 29* (Fig. 1) is believed to show ventricular tachycardia for the following three reasons: (1) the tachycardia failed to respond to vagal stimulation; (2) all recorded premature contractions before and after the paroxysm were ventricular in origin (wide complexes with compensatory pause as in Leads II, aV_L, V_1, V_3, V_5, and V_6 on March 29); and (3) the R-R interval was not absolutely regular during the paroxysm (best seen here in Lead V_6).

The causes of paroxysmal ventricular tachycardia as given in standard texts and collected series are[1-9]: (1) coronary atherosclerosis, especially after an acute myocardial infarction; (2) severe valvular heart disease, rheumatic or syphilitic; (3) severe hypertensive heart disease; (4) Wolff-Parkinson-White syndrome; (5) toxicity to digitalis or quinidine; (6) excitement, exercise, or emotional upset in an apparently normal individual; (7) thyrotoxicosis; (8) acute rheumatic fever; and (9) diphtheria or other acute infections. Individual case reports ascribe its occurrence to metastatic neoplasms,[10] Hodgkin's disease,[11] sarcoidosis,[12] idiopathic pericarditis,[13] and the use of anesthetics[14] or antimony compounds.[15]

None of these causes was found, although the effect of myxedema on the brain, the presence of a mild respiratory infection, and a possible mild or moderate degree of coronary atherosclerosis may have been significant.[4]

Sinus tachycardia, paroxysmal or chronic auricular fibrillation, and, to a lesser extent, other supraventricular tachycardias are very common in hyperthyroidism. However, only two cases with the combination of hyperthyroidism and ventricular tachycardia could be found in the literature. The first[17] was that of a 58-year-old Negro woman with a goiter, congestive failure, syphilis, a markedly enlarged heart, a basal metabolic rate of +38, and auricular fibrillation. In this patient a paroxysm of six successive complexes of ventricular origin was recorded. The second case[18] was that of a 44-year-old woman with auricular fibrillation, cardiomegaly, congestive failure, and goiter who was given large amounts of digitalis. As the ventricular rate decreased, premature ventricular contractions increased, culminating in runs of ventricular tachycardia. Both cases, then, were complicated by congestive failure and auricular fibrillation: one by syphilis and the other by digitalis intoxication. Several eminent cardiologists could not recall having seen the combination of hyperthyroidism and ventricular tachycardia.[19-22] One wonders whether hyperthyroidism alone is a cause of ventricular tachycardia.

Ullrick and Whitehorn,[23] using the tissue-slice technique with rat muscle, demonstrated that under the influence of thyroid hormone the basic respiration of auricular muscle (that is, oxygen requirement) is

more markedly increased than is that of the ventricular or skeletal muscle. Myocardial hypoxia increases myocardial irritability and the tendency to arrhythmia.[24] This relative sensitivity of the auricular musculature to the action of thyroid hormone offers a physiologic basis for the propensity to auricular tachycardias so characteristic of hyperthyroid heart disease. As far as is known, the converse experiments have not been made; i.e., the change in auricular and ventricular muscle respiration in hypothyroidism has not been noted.

The induction of the hypothyroid state with radioiodine has been found to reduce noticeably the incidence of supraventricular tachycardias in previously euthyroid individuals with rheumatic and arteriosclerotic heart disease.[25,26]

Sinus bradycardia and first-degree heart block are common in hypothyroidism and improve with the administration of thyroid extract. Other rhythm abnormalities, that is, paroxysmal auricular fibrillation, flutter and tachycardia, and nodal tachycardia have been reported in patients with myxedema. In these patients the abnormal supraventricular rhythms have, on occasion, reverted to normal after the administration of thyroid extract.[27-30] The inconstancy of this conversion and the presence of coexistent heart disease make it difficult to draw a cause-and-effect relationship.

Ventricular tachycardia has not, to my knowledge, ever been attributed to hypothyroidism, either spontaneous or induced. If ventricular tachycardia did occur in a patient with heart disease and induced hypothyroidism, it would probably be attributed to the underlying heart disease. As an example, Graybiel, White, Wheeler and Williams,[31] in their textbook of electrocardiography, show the tracing of a 45-year-old man on thiouracil. The electrocardiogram had abnormal T waves and short runs of ventricular paroxysmal tachycardia. The basal metabolic rate of their patient was −25 at that time. He had been thyrotoxic 4½ months before, at which time his electrocardiogram was borderline. Coronary artery disease was postulated as a possible explanation for the high degree of cardiac irritability. It is possible that the patient's hypothyroid state was also significant.

What caused the ventricular tachycardia in our patient? For the following reasons, myxedema is considered to be the primary cause of the myocardial dysfunction and resultant paroxysmal ventricular tachycardia. (1) A marked reduction in cardiac output and oxygen consumption is a consistent finding in myxedema.[32] Resultant myocardial hypoxia increases the tendency to arrhythmias. (2) The patient's premature ventricular contractions and abnormal electrocardiogram cleared promptly after the administration of thyroid extract and did not return. (3) No other cause of myocardial dysfunction or ventricular tachycardia could be found.

Although the causal relationship between hyperthyroidism and auricular tachycardias is firmly established, the relationship between hyperthyroidism and ventricular tachycardias is tenuous and may not exist.

Summary

A 42-year-old woman with myxedema and paroxysmal ventricular tachycardia is reported. Her electrocardiogram became normal, and premature ventricular contractions ceased after the administration of thyroid extract. In the absence of other known causes for the ventricular tachycardia, it seems likely that myxedema was the initiating cause. The relationship of the thyroid gland to cardiac arrhythmias is briefly discussed.

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Clinical pathologic conference

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Clinical abstract

The patient was a 24-year-old married woman who had one son, aged 2½ years. Her illness began in July, 1959, with symptoms attributed to influenza, namely, a hard, unproductive cough, dizziness, a feeling of heaviness in the head, generalized aches and pains, and retrosternal pain exacerbated by coughing and deep respiration. Such little expectoration as appeared was white, but it was occasionally streaked with blood. Tubercle bacilli were looked for but not found. The illness did not soon abate like influenza, but continued week after week. In August, she first noticed breathlessness and palpitation, at first only on exertion but later even on slight activity. After October, she coughed up no more blood for many weeks. In December, 1959, an x-ray film of her chest was made at a local hospital and was reported to show patchy consolidation at the left lung base and a minimal amount of fluid in the left pleural cavity (Fig. 1). Twice in December, and several times in January, 1960, she had further hemoptysis. In January, the appearance of her chest on the x-ray film was unchanged. The local doctor prescribed antibiotic capsules and 3 grains (0.2 Gm.) of thyroid daily. Return of the pain and also sweats, huskiness of the voice, and increasing breathlessness, so that she was a little breathless even at rest, and serious loss of weight, one stone (6 kilograms) in 3 months, led to her admission to hospital on February 2, 1960.

Her previous medical history mentioned "rheumatism" in the right wrist at the age of 10, since when this wrist had ached a little in cold weather, and also appendectomy at the age of 16. Menstruation was regular and normal, but the last period had been a week early and the flow scanty. During her pregnancy a negative blood Wassermann reaction had been recorded.

The family history mentioned a paternal uncle who had died of rheumatic fever, and a sister who had died of pneumonia. Her mother was under treatment for pernicious anemia.

Examination on admission revealed an anxious young woman, propped up on pillows, breathing shallowly and quickly (respiratory rate of 40 per minute). Her temperature was 100.4°F. (38°C.). Every now and then she had a paroxysm of hard, dry coughing, which caused her pain and distress. Her fingers were slightly cyanosed; but there was no clubbing.

Her chest movement was diminished on the left side. The breath sounds and the vocal fremitus and resonance were diminished over both lung bases posteriorly, and the percussion note was impaired. The chest seemed to be tender all over.

The pulse rate was 130 per minute, and the blood pressure was 115-75 mm. Hg. The apex beat of the heart was palpable in the sixth left intercostal space 3¼ inches (8 cm.) from the midline. The heart sounds were normal in so far as one could make out,

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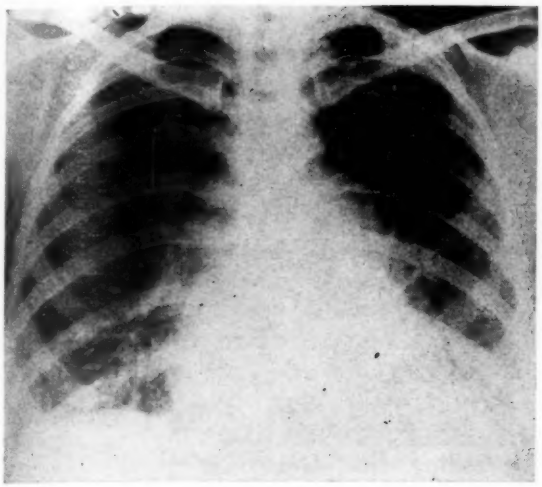

Fig. *1.* X-ray film of the chest taken on Dec. 26, 1959.

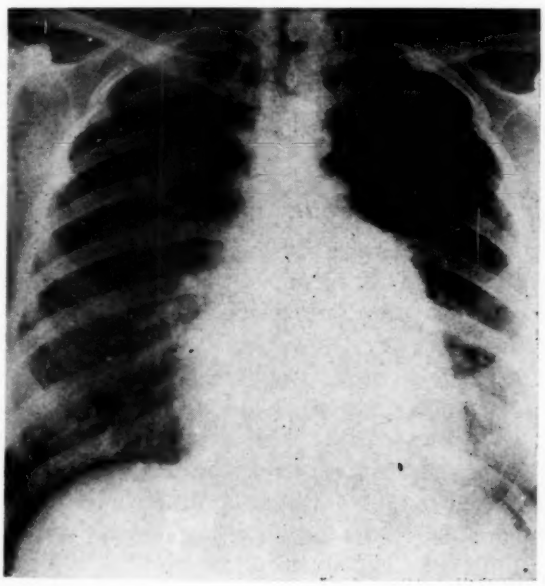

Fig. *2.* X-ray film on the chest taken on Feb. 3, 1960.

but a loud crunching pericardial friction rub was audible over most of the precordium.

No other abnormalities were discovered.

The results of laboratory investigations made in the hospital at the time of admission were as follows. *Blood:* Hemoglobin, 9 Gm. per cent; leukocytes, 18,500 per c.mm. (neutrophils 70, eosinophils 5, basophils 1, lymphocytes 14, monocytes 10 per cent). Of the neutrophils, 13 per cent were band forms. Sedimentation rate was 20 mm. in 1 hour (Hawksley tube, normal 4 to 8 mm.). No lupus erythematosus cells were found. The serum protein level was 6.6 Gm. per cent (albumin 3.4, globulin 3.2, no cryoglobulin). An intracutaneous tuberculin test gave no reaction. Sputum culture grew micrococci and green streptococci. The urine contained no albumin or sugar; microscopy showed only an occasional leukocyte. The antistreptolysin-O titer was 625 units per ml. X-ray examination of the chest (Fig. 2) showed slight enlargement of the heart, but considerable dilatation of the left atrium; also, there was hilar congestion and a little fluid at the left lung base. An electrocardiogram (Fig. 4) showed right axis shift but no other abnormality.

On February 3, the patient had a paroxysm of supraventricular tachycardia which lasted for several hours (pulse rate of 220 per minute), and which caused dyspnea and dilatation of the jugular veins. Digoxin was given in full dosage, with much improvement. Two days later she was able to sit comfortably in a chair by the bedside. Over the next few days, as the pulse became slower and as the pericardial friction diminished in loudness and finally disappeared, a soft systolic murmur of ejection type was heard to the left of the sternum.

On February 8, after the patient had complained of nausea for several days and had vomited, an intern reported that a mass was palpable above the pubes, but this observation was not confirmed by another examiner. A specimen of serum was subjected to the Galli-Mainini toad test for pregnancy, with a negative result. The same intern reported the mass again on February 19, when it was thought to be the urinary bladder.

By February 16, the patient felt much better, although the temperature usually rose above 99°F. (37.2°C.) in the afternoons. X-ray examination showed the heart to be a very little smaller and the lungs much less congested. However, low-pitched crepitations were audible at the left lung base. Palpation of the chest showed that the right ventricle was contracting more forcibly then normally, and the pulsation of the pulmonary artery could be felt. The palpable sensation due to the closure of the pulmonary valve was closely followed by another. At the left sternal border a presystolic sound was heard and a systolic murmur of ejection type. At the mitral area a third sound was heard early in diastole. The first sound was loud and clear.

During that night further hemoptysis occurred, and thence the patient's condition deteriorated, with increasing hemoptysis, orthopnea, and cyanosis.

Fig. *3.* X-ray film of the chest taken on Feb. 24, 1960.

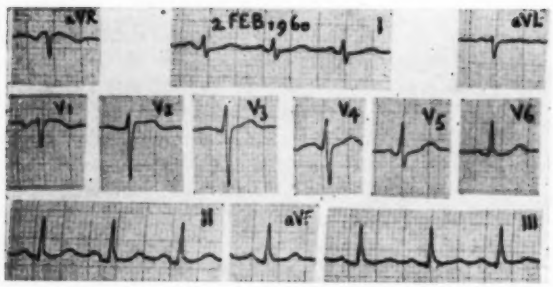

Fig. *4*. Electrocardiogram of Feb. 2, 1960.

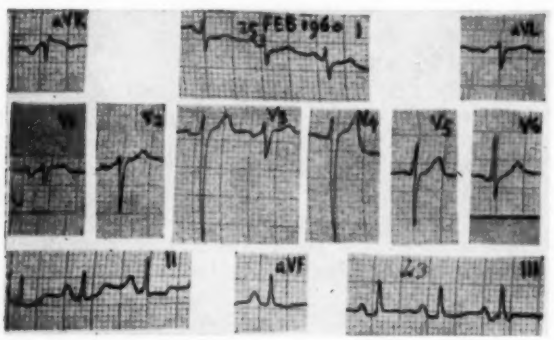

Fig. *5*. Electrocardiogram of Feb. 25, 1960, showing rapid onset of pulmonary hypertension.

On February 24, she had a copious hemoptysis. An x-ray film of the chest (Fig. 3) showed considerable dilation of the left atrium and pulmonary artery and a good deal of mottling in both lung fields, especially in the right. The small pleural effusion was still present at the left base.

On February 25, examination of the blood showed 11.2 Gm. per cent of hemoglobin and a sedimentation rate of 15 mm. in 1 hour; but the leukocytes numbered 60,000 per c.mm. (neutrophils 92, lymphocytes 5, monocytes 3 per cent; 20 per cent of the neutrophils were band forms). An occasional nucleated red cell was seen, as well as an occasional macropolycyte. An electrocardiogram showed an increase in the amplitude of the P waves, which were distinctly increased in duration in Leads V_5 and V_6 (Fig. 5).

The patient died on Feb. 25, 1960, and an autopsy was performed.

Discussion

DR. STUCKEY: I think it will be best first to take the general clinical features of the case and see what sort of picture is presented. We have a young woman who had been in good health. There seems to have been nothing of importance in her previous medical history or the health or her family. All at once she developed a progressive illness of about seven months' duration, which culminated in death. For a good deal of this time there was persistent low fever. Generalized aches and pains were present at the onset, and chest pains were mentioned at various stages of the illness. She complained of dizziness, and sweating at times, and there was substantial loss of weight. Those are the nonspecific features of the illness.

Next we come to a number of features which appear to be of respiratory origin. One of the most prominent of these was the persistent unproductive cough that she had throughout most of her illness. Another was the pleural (or possibly pericardial) pain: chest pain influenced by her breathing, and worse on coughing. Next was breathlessness, and this was an important symptom from quite early in the illness; from within about a month of the onset, it became progressively worse to the moment of death, with one intermission, which we will talk about, associated with therapy. Then there was hemoptysis: at first, slight and intermittent, a mere streaking of the sputum with blood, but in the later stages of her illness a dominant feature, not only more frequent, but more copious. The amounts were not mentioned, but I have the impression that this was quite substantial hemoptysis. Finally, we have the persistent clinical and radiologic signs of a localized lesion in the left lung, present from the beginning of her illness until her death, with not a great deal of change. There appeared to be radiologic signs of a lesion in the left lower lobe, and for most of the course of her illness there was a small pleural effusion. This important group of respiratory symptoms and signs appeared very early in the course of the illness and persisted to the end.

Then, late in her illness, cardiac signs became apparent. I will say no more about that at the moment, because I propose to analyze the cardiac features in more detail later on.

Next is the blood picture, which had three main features: anemia, leukocytosis with neutrophilia, and raised erythrocyte sedimentation rate. These features were present on at least two occasions when the blood was examined.

Finally, apparently unrelated to the other features, is the suggested presence of an intra-abdominal or pelvic mass. I

did not know what to make of this. It is said that one observer felt a mass, and that another did not. Apparently, pregnancy was suspected or thought of, because a test was made. In so far as we can gather, examination per vaginam was not carried out. This may well have decided whether or not a mass or other abnormality of the pelvic viscera was present. From the information that is presented to us, I do not think that we can draw any definite conclusions; so I will put it aside.

Now to consider some of the diagnostic possibilities of the general features of the illness that I have mentioned to you. Tuberculosis must be considered, but there are a number of things against it. Tubercle bacilli were sought for in the sputum and not found. The tuberculin test was negative at a fairly late stage of the illness, when the patient had been sick for 3 or 4 months, and this I think makes a tuberculous illness very unlikely. The site and character of the lesion in the lung are not those commonly found with tuberculosis, and this again is fairly strong evidence against it. Finally, cardiac involvement in tuberculosis is rare, apart from pericarditis. We have not analyzed the cardiac features yet, but there are some that suggest that more than the pericardium was involved. So, tuberculosis seems an unlikely cause of her illness.

Another possibility which we should consider briefly is bacterial endocarditis. There are some features here which suggest it: persistent fever, together with a cardiac lesion, anemia and neutrophilia. On the other hand, there are a number of features which make this diagnosis unlikely. There is no suggestion of systemic embolism in any shape or form. There is no record of enlargement of the spleen. No red cells were found in the urine. One would have expected, if this illness were bacterial endocarditis, that, at least in the late stages of the illness, substantial elevations of temperature would have occurred; and this did not happen. The low fever persisted to the end. Finally, we have the point that I have already stressed, that the predominant symptoms were pulmonary. We have a persistent pulmonary lesion there from the beginning to the end, so that my feeling is that bacterial endocarditis is a very unlikely possibility.

Another possibility to be considered is disseminated lupus erythematosus. There are some features that would fit in with this possibility: the fever and progressive downhill course of the illness leading to death, and the presence of a pulmonary lesion. There are many things that do not fit in. There was no exanthem at any stage of the illness, no manifestations in the joints. There was no leukopenia; on the contrary, there was considerable leukocytosis. Lupus erythematosus cells were looked for and not found, but we are not sure from the notes how extensive a search was made for the lupus erythematosus phenomenon. Finally, albuminuria was not mentioned nor any other evidence of renal involvement. Lupus erythematosus, then, seems to be unlikely.

Finally, we must, I think, consider a pulmonary neoplasm. The fatal outcome of the illness, the persistent local lesion in the left lower lobe throughout the whole course of the illness, the radiologic and clinical signs of involvement of the pleura (we have this suggestion of pleural fluid in the left pleural cavity throughout the entire illness, or through most of it), and the pericardial involvement, indicated by the quality of the chest pain and by the friction rub, all of these are consistent with the presence of a pulmonary neoplasm. In quite a substantial proportion of cases, neoplasms spread from the lungs to the heart. The proportion has been placed as high as 30 per cent of bronchogenic carcinomas at postmortem examination. Against this possibility we have the age and sex of this patient. Bronchogenic carcinoma is a great rarity in young women, so that one would think of the possibility of other forms of neoplasm; for instance, secondary neoplasm from some undiscovered primary site. So much for the survey of the general picture, without any particular accent on the cardiac findings.

I would like to turn now to the cardiac symptoms and signs, to analyze those in more detail, and see whether we can reach some more definite conclusion. There are a number of features here to mention.

First of all, there is the evidence of pericarditis, or pericardial involvement, which I have already mentioned. Secondly,

we have the paroxysm of tachycardia, apparently quite a severe attack, which lasted several hours and required treatment. Next we come to a group of symptoms and signs which, in combination, very strongly suggest the probability of mitral valvular obstruction. Progressive breathlessness on effort is one of these. Recurrent hemoptysis is another, and so is orthopnea. Those are the principal symptoms that suggest mitral valvular disease, or mitral valvular obstruction.

Then we come to some of the findings on examination which also suggest this possibility, and an important one is the left atrial enlargement seen on x-ray examination. I think perhaps that we could look at the x-ray films at this stage. These x-ray films are in time sequence. We have already talked about the persistence of radiologic signs at the left lung base. In the film dated February 3, which is by far the clearest (Fig. 2), there are still obvious abnormalities of the cardiac outline on the left side, and of the diaphragm, and some opacity in the left lung field, so that throughout the series we have persistent abnormality of the left lung. On the right side, on the other hand, the lungs appear to be normally clear in the earlier films.

Returning to the left atrium, I think that in this picture of February 3, there is suggestive evidence of left atrial enlargement. On February 13, it is more than merely suggestive; there is the appearance of double shadow within the right border of the heart, and prominence emerging from the left cardiac border. Elevation of the left main bronchus by the enlarged left atrium can also be seen. Thus, we have this important feature of left atrial enlargement shown by x-ray examination. This is a common and important sign of mitral valvular pathology. It is well to remember that this may occur to some extent in other conditions, not grossly but to some extent in any condition in which left ventricular hypertrophy occurs: hypertension, aortic valvular disease, and very large left-to-right shunts. In all these conditions, some degree of left atrial enlargement may occur, but there is nothing to suggest that any of them was in fact present in this particular patient. There is no history of hypertension or aortic valvular disease, and nothing to suggest any left ventricular stress, strain, or pathology that I can discover.

Hilar congestion is another radiologic sign of mitral valvular disease or obstruction, and this is very grossly present in the last x-ray picture of February 24 (Fig. 3), and it is also present to some extent, I think, in some of the earlier ones. This suggests obstruction of the mitral valve, elevation of pressures in the left atrium and pulmonary veins, and pulmonary venous engorgement and congestion of the lung.

The next important feature is in the electrocardiogram; there is a suggestion of right axis deviation, not very marked (Fig. 4). See how the P waves are increased in duration even in the first tracing, and in some there is even a suggestion of notching. I think that you will have difficulty in seeing the P waves about which I am talking, because they are not well shown in the complex selected. Now, an examination of the later tracing shows that there are definite changes from the earlier one. After only about 3 weeks the P waves are now tall as well as broad, and there is more right axis deviation than in the first record, and there is evidence of right ventricular preponderance, shown by the development of a secondary R wave in Lead aV_R and an S wave in Lead V_6.

Now, let us turn to the clinical signs, particularly the auscultatory signs. We are told that the first heart sound was loud and clear; this might be the accentuated, abrupt first heart sound of mitral stenosis. There is also mention of a third heart sound, and also of something felt in the pulmonary area after closure of the pulmonary valve. These two features, I think, could be an opening snap of mitral stenosis or some equivalent sound, coming fairly closely after the second heart sound. There is no mention in the notes of any diastolic murmur, and this is one of the features that I will comment on again in a moment. Finally, in regard to symptoms and signs of mitral valvular obstruction, I am very much impressed with the response to treatment with digoxin. There was a very good clinical response, according to the notes, and this is confirmed by the change in the radiologic appearances be-

tween February 3 and February 13. This is also suggestive of mitral valvular obstruction.

Finally, late in the illness, within the last week or two, there were signs of pulmonary hypertension: increased right ventricular activity on palpation, pulmonary arterial pulsations, palpable closure of the pulmonary valve, and an ejection type of systolic murmur heard at the left sternal border. We have noted that the main pulmonary artery was dilated in some of the x-ray pictures, and we have already noted in the electrocardiogram the increasing amplitude of the P waves. All these things suggest that, as a late feature, pulmonary hypertension developed.

I have one or two further comments to make on these features. We have already talked about the left atrial enlargement and its importance as a sign of mitral valvular obstruction. The P mitrale in the electrocardiogram has very much the same sort of significance, and, in my experience, it is a very useful sign, even in minor degrees. In general, as its name implies, it is associated with mitral valvular disease, but it may occur particularly in minor forms in any condition in which there is left ventricular stress or failure. There is nothing to suggest any of those features in this patient.

One or two other points remain for discussion. We might wonder why no auscultatory signs of mitral valvular disease were noted at the time of the patient's admission to hospital. I think that that is very understandable. We are told that at that time the patient had a loud pericardial friction rub, and this would drown out other sounds. Also, there was substantial tachycardia, which makes it very difficult sometimes to recognize signs of mitral valvular disease.

Another feature for comment is the absence of a mitral diastolic murmur. Is this consistent with the presence of mitral valvular disease? I think the answer is yes, in certain circumstances. In severe mitral stenosis the diastolic murmur becomes very soft and may be missed or not recognized; and in the presence of severe pulmonary hypertension the characteristic murmur of mitral stenosis may become soft, and may, in fact, disappear. I have seen several patients with severe mitral stenosis complicated by pulmonary hypertension in whom the diastolic murmur was absent. Therefore, the absence of a diastolic murmur of moment does not exclude the possibility of mitral valvular disease.

Finally, I think that we must consider the possibility of other causes of mitral valvular obstruction, apart from rheumatic mitral stenosis, particularly whenever the story is atypical, whenever there are unusual fluctuations in the usual signs and symptoms, or whenever the rapid progress of obstructive symptoms seems to be out of all proportion to the rheumatic process. We will come back to this point, but one of the impressive features of the illness was that the symptoms and signs of mitral valvular obstruction ran an extraordinarily fast course.

Let us now see whether we can correlate the cardiac and general clinical features. Is there any way we can correlate these so that they fall into some sort of pattern? There seem to me to be only two reasonable explanations to offer which would account for the manifestations we have described.

The first one is rheumatic heart disease—rheumatic carditis in the broad sense. Could this account for the entire illness, and all the manifestations of disease in this patient, and death? I think that it could, but there are many very unusual features about it. It is not common to find rheumatic carditis running a relentless downhill course ending in death in adult patients. One sees this picture occasionally in children. In adults it is an extremely uncommon finding. Usually when there is such an illness, the accent is on the myocardium rather than the valves. One sees the features of congestive heart failure, extreme cardiac enlargement, electrocardiographic changes which suggest myocardial disease, and so on. When the valves are involved, the type of involvement is usually incompetence rather than stenosis, and one would expect to find gross mitral incompetence rather than the features of stenosis that we have described. It is difficult to understand on a rheumatic basis the rapidly progressive mitral valvular obstruction that seems to have been present in this patient. Finally, we have the general

features of the illness which I have already stressed; they appear to be predominantly respiratory, certainly in the beginning and to some extent throughout the entire illness. There are many pulmonary complications of rheumatism, embolism, pneumonitis, and so on, but most of those are transitory. They come and go and resolution occurs, or they heal and disappear. Here we have the strong impression of some persistent and relentless lesion in the left lung throughout the entire course of the illness.

So, that brings us naturally, I think, to the other important path to take in trying to correlate these two approaches, and that is the question of pulmonary neoplasm as the possible explanation for the general features of the patient's illness. Could this be a neoplasm in the lungs, left lower lobe, with spread to the pleura, pericardium, and conceivably to the left atrial cavity, with mitral valvular obstruction? We know that this may occur occasionally; myxomas are the common tumors that occur in the left atrium. The main argument against this suggestion is the rarity of pulmonary neoplasms in 24-year-old women, and the much greater rarity of intracardiac spread of neoplasms. Undoubtedly, it might occur.

Therefore, in summation, my strong feeling is that there is definite evidence of progressive mitral valvular obstruction, with the late development of pulmonary hypertension, and, in my view, this cardiac lesion was the immediate cause of death. When we come to the more difficult question of underlying pathology, I feel that one cannot be dogmatic. There are two possibilities: first, progressive rheumatic carditis with mitral valvular obstruction and unusual pulmonary complications; and, second, pulmonary neoplasm, with spread to the pleura, pericardium, and the left atrial cavity, with mitral valvular obstruction. I find it difficult or impossible to decide between those two possibilities, but I feel very firmly that mitral valvular obstruction was present, and was the cause of death.

MODERATOR: Dr. Kalokerinos, Dr. Stuckey emphasized that throughout the entire series of x-ray films there was persistent abnormality at the left lung base. Would you look at this film of February 13, and tell us whether in fact this lesion has persisted at the lung base, or whether it has not temporarily disappeared in that film.

DR. KALOKERINOS: The lesion at the left base has certainly not completely cleared up, but it is much less distinct than in the earlier films. I think that we should presume that the opacity which we see at the left base has been due mostly to effusion, which has almost cleared up, but that there is underlying lung disease as well.

MODERATOR: What about rheumatic pneumonia? Do radiologists recognize it as an entity? Would it be a possibility in this case?

DR. KALOKERINOS: Yes, rheumatic lung is described. One may see pleural effusion, and areas of consolidation in the presence of rheumatic heart disease, usually in its acute phase, but the changes in the lung are not specific.

MODERATOR: One other point, if you will be so kind. The appearance of the right lung in the final film was described by Dr. Stuckey as hilar congestion and was also reported by the radiologist in those terms. Do you think that that appearance might be consistent with a pneumonic process? There was a very high leukocyte count at that stage.

DR. KALOKERINOS: I think that it was on the day after this film was made that the patient died. We are seeing a terminal phenomenon. We can see that the opacity is more marked in the medial half of the lung. It is not just vascular shadow. The appearance in the left lung field is somewhat similar, although not so well pronounced. It is not possible to state just what proportion of the opacity was due to edema of the lung, and what proportion to consolidation, but both are present.

MODERATOR: Dr. Epps, I did not see your name associated with this patient. Presumably you were not asked to perform cardiac catheterization in order to try to elucidate the cause of the mitral valvular obstruction. Do you think, taking into consideration this patient's pyrexia and the severity of her illness at the time, that cardiac catheterization would have been either feasible or helpful?

DR. EPPS: I think that there would have been some risk attached to cardiac cath-

eterization in this patient. It would appear that there was a considerable degree of pulmonary hypertension in the latter portion of the illness, and it is well recognized that cardiac catheterization in patients with severe pulmonary hypertension carries some risk. I think that it is an acceptable risk, just as there is a risk in patients with severe cardiac failure.

The primary purpose of a catheter here, I think, would have been to confirm or refute the suggestion that there was mitral valvular obstruction. I feel, as Dr. Stuckey does, that there is very strong presumptive evidence of mitral valvular obstruction in this case, and I think that the catheter would have afforded a critical test of that evidence.

There is one other way in which the catheter might have been helpful, and that is in detecting a thrombosed pulmonary artery. Looking at the x-ray films, I am very much impressed with the rapid increase in the size of the pulmonary artery, and I am also impressed with the clinical and electrocardiographic evidence of a rapid onset of pulmonary hypertension. In fact, it was so rapid that it may not have been due entirely to mitral valvular obstruction, but partly to something else in the lungs, or pulmonary vessels. Maybe there were multiple emboli or infarcts occurring in the lungs, or even thrombosis of pulmonary arteries. If we had passed a cardiac catheter into each of the pulmonary arteries, we could have said at once whether or not one or the other of them was obstructed.

MODERATOR: One other interesting feature here that we have not yet brought out is that there was a very high leukocyte count: 60,000, on the day before the patient's death. I wonder whether you would like to say anything about that, Dr. Durie.

DR. DURIE: Leukocytosis was present when the patient first entered the hospital, and this final, very high count was probably due to an exacerbation of whatever caused leukocytosis in the first place. Such a high count is sometimes called a leukemoid blood picture, and here it does deserve that name. It could be caused by a severe infection, or by toxemia of some kind, although much more rarely, or by an intoxication with some drug. It sometimes occurs in malignant disease, even without bone involvement, especially if there is necrobiosis.

MODERATOR: Could the electrocardiograms be projected? Would you care to comment on them, Dr. Freeman.

DR. FREEMAN: Between the time of these two electrocardiograms, which were taken about 3 weeks apart, there is a considerable change. We know that when this earlier tracing was taken, she had quite marked left atrial enlargement, and we see here a slight increase in the P wave in Leads II and III. There is quite definite right axis deviation; in other words, the main vector is about +90 degrees, which in an adult is suggestive evidence, but not proof, of right ventricular hypertrophy. Apart from minor P-wave changes, there is nothing else of any note in the first tracing. But after just over 3 weeks, we see distinct changes; the right axis deviation is a little greater and we see signs which are suggestive of those which are found in anoxic pulmonary heart disease or cor pulmonale. These signs consist of five findings: a large P (a Gothic type of P very often), which is most marked in Leads II, III, and aV_F, and which is quite definite in the second tracing; the T_a wave which is evident here, comprising a 1-mm. depression of the T_a wave in Lead III, and which is also seen in Lead II; right axis deviation, which we have already noted; clockwise rotation of the heart, which is more evident in the later tracing, with an S wave in Lead V_6; and a low R wave across the chest.

All these things indicate an obstruction to the right ventricle, in other words, pulmonary hypertension. Hence, it is a very interesting tracing, in that we see a most abnormally rapid development of electrocardiographic signs of right heart strain, or right ventricular hypertension.

MODERATOR: Dr. Freeman, would you explain what you mean by the T_a wave.

DR. FREEMAN: It occurs during the P-Q interval. During this interval the galvanometer does not register exactly zero potential because of atrial repolarization, and its deflection from the isoelectric level is opposite in sense to the P wave.

MODERATOR: So far as we have gone, Dr. Stuckey has arrived at a provisional diagno-

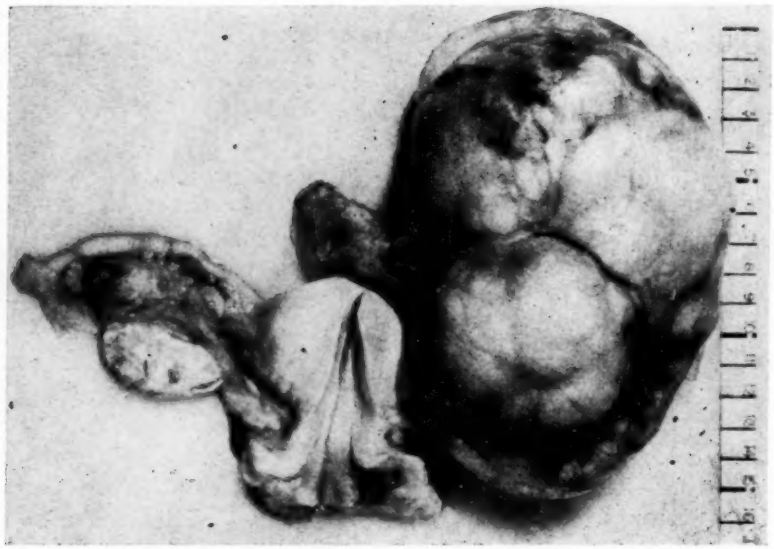

Fig. *6.* Uterus and adnexae, showing the tumor of the left ovary.

sis of mitral valvular obstruction and pulmonary hypertension, due possibly either to rheumatic heart disease or to pulmonary neoplasm. Dr. Epps has added to that the possibility of thrombosis in the pulmonary circulation. Is there anyone else who would like to make any suggestions or comments on what has gone before?

DR. KRAUS: We have the heart syndrome, the lung syndrome, and the temperature. It all fits in well with mitral stenosis and superimposed bacterial endocarditis. We have no result of blood cultures, but we have a high antistreptolysin titer; so, we are able to suggest bacterial endocarditis.

MODERATOR: Dr. Kraus has drawn attention to the high antistreptolysin titer.

DR. STUCKEY: I found this very difficult to interpret. It was done at a late stage of the patient's illness. This can be a useful diagnostic test in the early stage of an illness which may be rheumatic fever. Its significance is that there has recently been a streptococcal infection, particularly if there is a rising titer over a few weeks. The significance of this particular test which was made some 4 months after the onset of the illness I just do not understand. The figure given is abnormally high, but I find it difficult to place very much reliance on that test at that particular time, either for or against a rheumatic etiology.

MODERATOR: Any further suggestions?

DR. FREEMAN: One of the things to be thought of is the possibility of a mycotic infection of the lungs, such as by Monilia. These sometimes spread from the lung to the pericardium, and might perhaps affect the heart. Another condition that crosses my mind is Wegener's granulomatosis or polyarteritis nodosa of the lung. Whether that could cause such grave obstruction I do not know. Another thing is the possibility of chorionepithelioma metastasizing to the lung and to the heart, because there was a question here of a pelvic mass.

MODERATOR: Yes, and there was an irregularity of menstruation.

MR. RAVEN: I would like to suggest an infiltrating lesion of the mediastinum—I thought of Hodgkin's disease because the patient was a young woman and there were signs of involvement of the left atrium, pleura of the left lung, and pericardium. Also the anemia, fever, loss of weight, terminal leukemoid reaction, and the persistent eosinophilia were suggestive of Hodgkin's disease. Although there were no signs elsewhere of the disease, Hodgkin's disease can remain localized to the mediastinum.

MODERATOR: Are there any other contributors before we call on the pathologist to tell us the answer? I am very sorry to say that Dr. Colin Graham was unable to be present at this conference, but Dr. Jones has more than kindly taken his

place at short notice, and I understand did have some knowledge of this patient's case when the autopsy was performed.

DR. JONES: The autopsy was carried out 25 hours after death. The body was that of a slightly obese young woman. There were no scars. The thyroid, larynx, and pharynx were normal. The peritoneal cavity and the abdominal viscera were normal, except as I shall tell you. The liver showed slight evidence of congestion, but was otherwise normal. The spleen was normal in size. The right suprarenal gland was normal. The left suprarenal gland was normal, but beside it was a nodule, 1.5 cm. in diameter, whose cut surface was homogeneous. Several of the retroperitoneal lymph glands were slightly enlarged and had similar homogeneous cut surfaces. The cervix and body of the uterus were normal.

The tubes and right ovary were normal. The left ovary was replaced by a large tumor, 15 by 9 by 9 cm. in size, which had a lobulated appearance (Fig. 6). It felt semisolid, and when cut was seen to have undergone postmortem degeneration. The more solid parts appeared white and homogeneous. The tumor appeared to be perfectly encapsulated. Its attachments were those of a normal ovary. There was no involvement of the local lymph glands.

The pleural cavities each contained one or two fluid ounces of a straw-colored fluid. There were adhesions between the parietal and visceral pleura of the left side at the apex and on the diaphragmatic surface. These were dense but of small area. There was a nodule, 1 cm. in diameter, on the lateral surface of the lower part of the left lower lobe. It was in the lung tissue, but just beneath the pleura. The esophagus was normal. At the bifurcation of the trachea was a small amount of blood-stained fluid, which appeared to be coming mostly from the right side. The left bronchus contained mucoid material and had been moderately compressed by grossly enlarged tracheobronchial lymph glands. There were some small nodules along the peribronchial lymphatics. The lung was aerated throughout, but there was a small infarct in the left lower lobe. There were no abnormalities in the lung tissue which underlay the adhesion previously mentioned.

There were several enlarged homogeneous lymph nodes—these were smaller than the ones on the left side. The right upper lobe was normal. The right middle lobe was consolidated to a moderate degree. The right lower lobe was entirely consolidated and sank when placed in formalin. The venae cavae were normal. The pericardial cavity was completely obliterated by nodules of tissue with homogeneous surfaces. Between the nodules was fibrinous material. The larger nodules were situated on the left side of the pulmonary artery and immediately between the pulmonary artery and the aorta. They extended into the wall of the left atrium. The pulmonary artery had been moderately compressed by the tumors. The left atrial cavity had been invaded by a lobulated piece of tumor which had obliterated its lumen to a marked extent and probably prevented efficient contraction. This piece of tumor extended down to and just through the mitral valve. The tumor which passed through the mitral valve caused some obliteration of the orifice of the valve

Fig. 7. Heart laid open to display the cavities of left atrium and ventricle, showing metastatic tumor with shining surface, almost filling left atrium and extending through mitral orifice into the ventricle.

and also prevented the cusps from closing adequately. This slide (Fig. 7) shows the tumor in the atrium and projecting down into the orifice of the mitral valve. The right ventricle was slightly hypertrophied. The right atrium and the left ventricle were normal. The other valves were quite normal. The coronary arteries were normal, and the aorta showed a little atheroma. The breasts were normal. The brain was not examined.

Microscopically, the ovarian tumor proved to be a very cellular sarcoma, with pleomorphism of the cells and nuclei. There were areas of mucoid degeneration. The right middle lobe between areas of consolidation showed extravasation of blood into the alveoli. The right lower lobe was consolidated and appeared in the stage of gray hepatization.

The hilar and upper abdominal nodes examined showed a sarcoma similar to that in the ovary. The tumor which invaded the left atrium showed the same histologic picture, and areas of it had undergone infarction.

MODERATOR: Dr. Stuckey told us that a neoplasm within the chambers of the heart would be a rarity indeed.

DR. LLOYD: I am sure that many people would agree that neoplasm of the heart, either primary or secondary, is extremely rare, but, on reviewing the literature, we find that in the experience of pathologists it is relatively common. Beginning about 1856, the pathologists started reporting long series of cases in which the incidence of secondary involvement of the heart was as high as 0.5 per cent of all autopsies, and about 6 per cent of cases of disseminated malignancy. The frequency with which these cases has been reported has grown. Up to 1908, 150 cases of secondary neoplasm of the heart had been reported; but in the 7 years following 1931, there were 200 cases reported. However, they were all diagnosed postmortem, and to bear out this fact was a figure that up to 1950, only 20 cases of malignancy of the heart had been diagnosed antemortem; so I think that it is certainly excusable that in this case the diagnosis was not exactly pinpointed either while the patient was in the hospital or by Dr. Stuckey in his very good discussion of the case.

A few other points about secondary malignancy of the heart should be made. It is generally accepted that the right side of the heart is more commonly involved than the left. The reason for this appears to be that 75 per cent of the coronary arterial blood returns to the right side of the heart. The valves themselves are very rarely involved, and when they are involved, do not usually cause obstruction. The endocardium is also involved rarely, and, when it is, it can be involved in either of two ways. As in this case, the growth may invaginate the endocardium, and so have a glistening appearance. I think you will agree from the slide that this tumor was quite shiny. Then, the endocardium may receive direct deposition of tumor masses, which are accordingly rough, and these may have blood clot superimposed on them, and simulate very exactly subacute bacterial endocarditis. The case most closely resembling this one, that I can find, was reported by Wainwright in 1938. It was a case of secondary sarcoma of the lung. The growth had extended from the lung down the main pulmonary vein, and had gone right through the left atrium and through the mitral valve. I could find no case in which there had been a secondary deposit causing a mitral stenotic type of lesion.

The primary site of tumors causing secondary involvement of the heart may be in any organ of the body; the most common one is the lung, and that is closely followed by the breast.

One thing which is apparent in the literature, and which is brought out very well in this case, is the extensive involvement of the heart that may occur before decompensation sets in. This girl went on for several months without a great degree of disability. Admittedly, she was a good deal restricted, but one is amazed that the heart managed to work at all, when one considers all the findings which we have discussed here.

Other points that were made in the extensive available literature were that again it is an extremely difficult condition to diagnose if there is no primary neoplasm which is obvious—as in this case. It is important to bear in mind the diagnosis of this type of condition when there is un-

explained heart disease, with no history of rheumatic fever and no coronary disease, and particularly when there is a pericarditis, or pericardial tamponade, or an arrhythmia of any kind, or congestive cardiac failure which is progressive in spite of treatment.

Clinical diagnosis. Mitral stenosis: rheumatic carditis.

Dr. Stuckey's diagnosis. Mitral valvular obstruction and pulmonary hypertension due either to rheumatic heart disease or pulmonary neoplasm.

Other suggested diagnoses. Pulmonary thrombosis (Dr. Epps); Wegener's granulomatosis or chorionepithelioma (Dr. Freeman); subacute bacterial endocarditis (Dr. Kraus); Hodgkin's disease of the mediastinum invading heart and lung (Mr. Raven).

Anatomic diagnosis. Sarcoma of left ovary, with secondary deposits in the heart, obstructing the mitral valve, and in the lung, pleura, and tracheobronchial lymph glands: pulmonary thrombosis: pneumonia.

Annotations

Mathematical physics and the physician

One of the facts of life is that in only a few specializations, among them the cardiovascular, is the background of physicians in mathematics and physics totally inadequate; in most of the medical field (general practice, surgery, obstetrics, pediatrics, psychiatry, the greater part of internal medicine, etc.), hardly any or no mathematics at all is needed. The consequence of this is that it is impractical and certainly impossible to adapt the curriculum to the needs of the relatively small group. This is especially so since these needs are far greater than is generally realized. The only thing that could be done, and which has sometimes been tried without success, is to supply the needs of the small group during the time of their specialization. Why did these attempts fail in most cases? Chiefly because the problem of time involved is usually underrated by teachers and students. Because we do not like unpleasant facts, we close our eyes to them. It is an unpleasant fact that nowadays for fruitful research in several medical fields a background in classic physics is needed that is equivalent to that of the well-trained physicist. When the physician cannot acquire this background in a few hours, he is inclined to lose courage and quit. Practically always the teacher has to try to take a shortcut and teach all the necessary mathematics in a very short time by giving a so-called "popular" course, which actually is more a course in mystics than in mathematics. We need not wonder that the only result is a well-cultivated inferiority complex among the students. When the course is rigorous and good, the result is nil also, because our medical doctors are not mentally prepared for the amount of self-study and homework that is required.

Μη εἶναι βασιλικην ἀτραπον ἐπι γεομετριαν. "To mathematics there is no path for kings," and I would like to add, not even for doctors! When a young doctor wants to specialize and do research work in the cardiovascular field, he has to be prepared to follow during the first four years of his training three hours of rigorous mathematics and physics lectures per week, lectures that will require from him at least 2 hours of intensive homework per day, weekends not excluded! How this has to be fitted into his schedule is his problem and that of the chairman of the department. It is a pity if this problem cannot be solved, for then we have to be satisfied to gradually leave more and more of our research to physicists who are willing to spend an equivalent amount of time acquiring knowledge in the cardiovascular field. Teamwork between a physician who knows nothing about physics and a physicist who knows nothing about medicine may seem an attractive substitute, but it does not work. Teamworkers have to understand each other's language and problems thoroughly. Our young cardiologists have to take the whole dive into the mathematical ocean; just dipping their big toe into the water will not be sufficient.

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Etiology of pre-eclampsia eclampsia

The etiology of specific hypertensive disease of pregnancy has long remained an enigma. Although eclampsia has been recognized as a clinical entity from antiquity, the primary pathogenetic factor has escaped detection despite extensive clinical study. During the nineteenth century, eclampsia was variously regarded as a form of Bright's disease, as a primary disease of the liver, and even as a condition comparable to parturient paresis in cattle. The latter concept led to the practice of mastectomy as a therapeutic measure, as advocated by Sellheim.[6] With the development of a satisfactory practical technique for measurement of blood pressure at the turn of the century, pre-eclampsia was recognized as a hypertensive state preceding the development of convulsions or coma. Subsequently, Volhard,[8] in 1918, properly emphasized the primary vascular nature of pre-eclampsia eclampsia. However, until recent years a confused state of affairs relative to etiology and diagnosis persisted, as evidenced by

the inclusion of acute yellow atrophy of the liver, pernicious nausea and vomiting, various renal afflictions, as well as certain hypertensive states peculiar to pregnancy, in the category of "toxemia." In clinical thinking, the etiological factor common to these various entities was considered to be a toxic material (hence toxemia), a concept culminating in the studies of the Smiths[7] concerned with the identity of such a substance which presumably was elaborated because of errors in hormone metabolism.

A number of authors, including Bastiaanse,[1] Brust and co-workers,[2] Kellar and Sutherland,[4] have suggested that a pressor substance was responsible for the vascular phenomena basic to the toxemic complex. The possible relation of placental ischemia to the production of a humoral agent has been discussed by Page,[5] but the identity of such a compound or isolation of a pressor material from pregnant animals or the products of conception have been notoriously unsuccessful. However, the recent observations of Hunter and Howard[3] indicate that such a pressor material may be consistently isolated from the decidua and amniotic fluid of patients with toxemia, but not from normal pregnant subjects. These findings, if confirmed, may represent a most significant contribution to our understanding of the pathogenesis of acute toxemia of pregnancy.

Hunter's active material has been termed "hysterotonin." Preliminary studies suggest that it is a polypeptide of large molecular size, the activity of decidual extracts not being decreased by dialysis. It is lacking in antidiuretic activity and is apparently distinct from angiotonin as well as other polypeptides which produce pressor responses. The active principle is thermostable between pH 3.3 and 8.3 and is rapidly inactivated by kidney extracts, but the pressor activity is potentiated by incubation with plasma. The authors suggest, on the basis of their experimental observations, that hysterotonin is produced by an enzymatic reaction according to the following scheme: Enzyme (in decidua) + Protein (in plasma or amniotic fluid) → Hysterotonin.

In consideration of the many disappointments of the theorists over the years concerning the etiology of the specific hypertensive diseases of pregnancy, optimism must be guarded in acceptance of new data bearing on this problem. However, it is hoped that the chemical characterization as well as the kinetics of production of Hunter's pressor substance will be forthcoming with continued investigation of what may historically be regarded as a major contribution to reproductive research.

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Steroid maintenance treatment in cor pulmonale

Although antibiotic therapy has reduced the hazards of acute infection in patients with chronic bronchitis and asthma, it has, by prolonging their lives, encouraged an increased incidence of chronic cor pulmonale and the prospect of progressive invalidism.

Experimental, pathologic, and clinical evidence[1-4] indicates that two basic mechanisms, acting alone or in combination, are responsible for this cardiac disability: (1) alveolar hypoventilation with anoxia and hypocapnea inducing pulmonary vasoconstriction, hypervolemia, and increased cardiac output, and (2) anatomic reduction of the pulmonary vasculature. The evidence also suggests that the former is probably the more important mechanism.

Thus, acute bronchial infection and emotionally induced asthma, disorders more likely to aggravate anoxia than to accentuate vascular damage, frequently precipitate congestive failure in patients with chronic cor pulmonale; and the absence of cor pulmonale in patients after pneumonectomy indicates that pulmonary vascular destruction must be extensive before it contributes to the development of this condition. Furthermore, emphysematous

patients dying with cor pulmonale often have comparatively little destruction of lung vasculature but prominent signs of respiratory obstruction in the form of bronchitis, bronchiolitis, and bronchopneumonia.

Such evidence, however, does not exclude the functional effect of increased intra-alveolar pressure in emphysematous subjects; when communicated to the pulmonary capillaries, this increased pressure raises pulmonary vascular resistance and elevates pulmonary arterial pressure. Nor do pathologic changes take into account the respiratory pump, which influences pulmonary arterial pressure by varying the stroke output of the right ventricle; in this respect, wide fluctuations in pulmonary arterial pressure associated with increased respiratory excursion have been reported in patients with chronic pulmonary heart disease.[5]

The reversibility of the pulmonary hemodynamic consequences of anoxia by adequate oxygenation[3] favors the view that anoxia is of major importance in the development of cor pulmonale and emphasizes that relief of anoxia must be the prime consideration in the treatment of this condition. Requirements for oxygen can be reduced with bed rest and antithyroid drugs, and oxygenation improved by maintaining a free airway with antispasmodics and expectorants combined with antibiotic treatment. These measures may be supplemented by intermittent oxygen therapy, and, when heart failure is present, by digitalis, diuretics, and salt restriction also. Venesection, to reduce the hematocrit level to between 45 and 50 per cent without lowering the hemoglobin below 12 Gm. per cent, may be of some value. Sedation should be avoided, because it encourages anoxia.

Steroid drugs might be expected to benefit asthmatic patients with cor pulmonale, since, as well as increasing oxygenation by improving pulmonary ventilatory capacity,[6] they will relieve acute asthmatic attacks, and, by thus correcting acute anoxia and simultaneously reducing respiratory efforts, they would remove two of the major factors promoting pulmonary hypertension. Furthermore, the ability of long-term steroid therapy to prevent or to greatly reduce the frequency and severity of acute asthmatic episodes in patients with chronic asthma[7-11] suggests that this treatment might prevent or delay the development of cor pulmonale in such patients.

Although steroid drugs have been advocated in the treatment of chronic cor pulmonale,[12] some[4] consider the benefits to be outweighed by the possible adverse side effects,[8,13,14] especially when usage is continued for long periods.

That long-term steroid therapy may be of value in certain patients with cor pulmonale is evident from a recent report.[15] Four patients with bronchial asthma received prednisolone for periods which varied from 9 to 18 months; 3 of the patients had clinical and electrocardiographic evidence of chronic cor pulmonale, and 2 of these were in heart failure when steroid treatment was started. The symptomatic relief induced by this treatment was maintained in these 3 patients, whose exercise tolerance was so improved that each was able to lead a normal life of unrestricted activity. No less gratifying was the objective improvement; coexistent heart failure promptly subsided (in one case, congestive failure was resistant to standard treatment), rhonchi disappeared, and in each instance the abnormal electrocardiographic patterns reverted to normal.

Patients in this series also had certain features which suggested a state of adrenocortical insufficiency, and this clinical premise was supported by biochemical evidence which further indicated that such insufficiency was due to decreased activity of the anterior pituitary gland. It was argued, therefore, that, in addition to the reasons already advanced in favor of long-term steroid therapy, such treatment, as substitution therapy, was indicated in these patients in order to correct an endogenous deficiency. This reasoning was favored by the fact that improvement was achieved and maintained by physiologic (prednisolone, 7.5 to 12.5 mg. daily) rather than pharmacologic dosage, and perhaps also by the diuresis[16,17] which the patients exhibited and which has previously been reported in asthmatic patients[18] during steroid treatment.

As might be expected with physiologic steroid dosage, adverse side effects did not occur; the dosage was increased by 5 mg. daily during intercurrent infection, and the patients were warned that extra steroids would be necessary, with expert supervision, should they be exposed to particular hazards—for example, general anesthesia.

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Masked thyrotoxicosis and coronary artery disease in father and son

A familial factor is common in many constitutional diseases. Sometimes this is quite strong and dominant and at other times it is less impressive. Hyperthyroidism belongs to the latter type.[1] The same is true of coronary artery disease. There certainly are families that have more than their share of angina, coronary thrombosis, or sudden unexpected deaths. It is also true that relative antagonisms exist between one disease and another. In the "preliver days" it was extremely rare to see hypertension in a patient with untreated pernicious anemia. Coronary thrombosis is less common in patients with alcoholic cirrhosis than in the general population at the same age level.[2] Likewise, angina pectoris or coronary thrombosis is comparatively rare in those who have hyperthyroidism at the same time.[3] This does not mean that the two states do not occur together. I have seen a small number of such cases, but in an extensive experience with coronary disease the simultaneous presence of both coronary disease and hyperthyroidism has not been frequent.[4,5]

Many years ago (Dec. 27, 1928), I examined a 52-year-old man who complained of pain in the right anterior chest, coming at rest and on effort, lasting several minutes or even as long as one-half hour, and at times radiating down both arms. This began about 2 months previously and had been growing worse. He was sent to the hospital for more careful observation. Because of the appearance of the face (salmon-colored skin), a unilateral stare, and an unexplained insidious loss of 35 pounds of weight during the previous months, I suspected that he had hyperthyroidism. The basal metabolic rate was +33 per cent. Because he had no exophthalmos or palpable thyroid gland and had a regular heart rate of 70 or less, neither the physicians on the medical service nor the surgeons would accept this diagnosis of hyperthyroidism. He was thought to have suffered a coronary thrombosis during the early days of the hospitalization, because of a slight fever and leukocytosis and definite transient inversion of the T wave in Lead I of the electrocardiograms (only three leads were taken in 1928). He continued to have anginal attacks at rest in bed, which were promptly relieved by nitroglycerin, until he was given a course of Lugol's solution. The angina then promptly improved but did not disappear entirely. I had no doubt about the diagnosis of thyrotoxicosis all this time. He was then given a course of x-ray treatment over the thyroid region; the Lugol solution was discontinued, and he was discharged to the outpatient heart clinic. However, the anginal state grew worse, and he was sent into the surgical service for a subtotal thyroidectomy. Immediately after this operation the angina vanished and he carried on satisfactorily.[2] He died 17 years later, in 1945, at the age of 69 years.

Thirty-one years after the above-mentioned experience (Dec. 26, 1959), I saw another patient in a neighboring hospital who complained of pain to the right of the mid-sternum. This was a choking sensation which came on generally at rest and often radiated into both arms and hands. He was given digitalis by one physician, which made the condition worse. The spells were helped by nitroglycerin. Sometimes he would use about 20 nitroglycerin pills during the day and 10 at night. Ordinary physical examination was entirely negative. Without any knowledge of the events soon to be described, I noted that the patient had a peculiar salmon-colored skin, and I therefore thought about the possibility of hyperthyroidism. It then occurred

to me that the patient's name was familiar to me. It developed that he was the son of the man whom I had examined 31 years before, whose history was discussed above. Here we had father and son with the same condition. As in the first case it was also difficult to convince his physician that we were dealing with masked thyrotoxicosis. Some days thereafter he suffered a definite coronary thrombosis, from which he recovered. The laboratory data supported the diagnosis of thyrotoxicosis. The blood cholesterol was 140, the radioactive iodine uptake was 59 per cent, the red blood cell radioactive iodine uptake was 23.8 per cent (normal = 14-18 per cent), protein-bound iodine was 16.0 micrograms per cent, and the basal metabolic rate was +17 per cent. He was later given 5 millicuries of radioactive iodine, and he made an excellent recovery.

Father and son had a similar and uncommon combination of conditions. They both had masked hyperthyroidism and angina pectoris. In both the pain was in the right rather than in the left chest. In both instances it was not easy to convince the attending physicians that thyrotoxicosis was present, because exophthalmos was absent and a palpable thyroid gland could not be made out. A clue to the diagnosis was the peculiar salmon-colored appearance of the skin of the face. Finally, in both instances, dramatic improvement in the angina resulted on appropriate treatment for the thyrotoxicosis.

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Book reviews

SURGERY OF THE AORTA AND ITS BRANCHES. By James D. Hardy, M.D., M.S. (Chem.), F.A.C.S., Professor and Chairman, Department of Surgery, University of Mississippi Medical Center, and Surgeon-in-Chief to the University Hospital; Chief Surgical Consultant, Veterans Administration Hospital, Jackson, Miss. Phiiadelphia, 1960, J. B. Lippincott Company, 386 pages. Price $6.50.

A series of articles on acquired diseases of the aorta and its branches appearing in the *American Practitioner and Digest of Treatment* serves as the nucleus for this volume. The intent of this book then is to offer additional familiarity and information regarding diseases of the aorta and peripheral arteries to physicians engaged in the general practice of medicine and surgery. The various chapters, therefore, are particularly informative with regard to diagnosis of arterial diseases and indications for surgical treatment. Controversial aspects concerning the kind of surgical treatment which should be employed are largely avoided. The chapters on diseases involving the arterial supply to the upper extremities and on peripheral arterial embolism are especially interesting and informative. This book would probably not be sufficiently detailed for use by a specialist in the field of arterial diseases, but does serve as a worth while source of information for those segments of the medical profession to which it is specifically directed.

NATURE OF RHEUMATIC HEART DISEASE. WITH SPECIAL REFERENCE TO MYOCARDIAL DISEASE AND HEART FAILURE. By George E. Murphy, M.D., Department of Pathology, the New York Hospital–Cornell Medical Center. Reprinted from *Medicine*, Volume 39, Number 3, September, 1960, Baltimore, 1960, The Williams & Wilkins Company, 343 pages, 162 photomicrographic illustrations in color. Price $3.50.

The basic theses of this monograph are that rheumatic heart disease in man is not a collagen disease, but a heart muscle cell disease, and that the involvement of the myocardium is a strong contributing, if not the main, cause of death in this disease in children and adults.

These theses are arrived at by a histopathologic study of the disease in the entire heart and in left atrial biopsies in man, and by an experimental production and histopathologic study of a rheumatic-like disease in random, and specially bred, rabbits. The disease in rabbits was produced by repeated focal cutaneous infection with different types of Group A beta hemolytic streptococci at monthly intervals for 6 months or a year. Some rabbits developed dyspnea, leukocytosis, rapid irregular pulse, and raised sedimentation rate, and died within 4 to 14 days. In these rabbits, endocardial and myocardial lesions were produced which the author believes bear a striking histological and cytological resemblance to those of rheumatic heart disease. The author brings evidence that these Aschoff-like bodies originate and evolve from rheumatic injury to heart muscle cells, and not from injury to connective tissue. From a study of both human and animal material, he believes that he has evidence for the origin of Aschoff bodies from myocardial muscle cells, and from smooth muscle cells of the endocardium, valves, and intramyocardial coronary arteries. From a study of the lesions in atrial biopsies, he finds a close correlation between the occurrence of specific rheumatic lesions in the atria and the presence of Aschoff bodies in the ventricles. Thus, he believes that active rheumatic myocardial disease in man is an important factor in all ages for the embarrassment of cardiac function, and heart failure.

The author presents an excellent review of the literature on the nature of rheumatic fever, the Aschoff body, and the experimental production of rheumatic-like disease in animals. He devotes considerable space to the difference of opinion between Saphir and himself as to whether the lesions produced by him experimentally are truly Aschoff bodies, and as to whether these bodies originate from myocardial muscle cells. One hundred sixty-two exquisite photolithographs document the presentation.

This monograph is a *must* for all those interested in heart and collagen disease. It would appear that the author has produced a disease in rabbits which closely resembles rheumatic fever. In view of the criticism of Saphir, it would also appear that the thesis that the Aschoff body originated from myocardial and smooth muscle cells of the heart requires further study.

RESUSCITATION OF THE NEWBORN INFANT. PRINCIPLES AND PRACTICE. Edited by Harold Abramson, M.D., Professor of Clinical Pediatrics, New York Medical College, New York; Director of Maternal and Child Health Program, New York Medical College–Metropolitan Medical Center, New York; Attending Pediatrician, Flower and Fifth Avenue Hospitals, New York; Visiting Pediatrician, Metropolitan Hospital, and Chief, Communicable Disease Service, Metropolitan Hospital, New York; and formerly, Epidemiologist, Bureau of Preventable Diseases, New York City Department of Health. St. Louis, 1960, The C. V. Mosby Company, 274 pages. Price $10.

This is an excellent book for all who are concerned with the newborn infant and his problems of survival. The book could be better titled *Pathophysiology of the Newborn* with an emphasis on the respiratory system, and it represents the most up-to-date collection of knowledge of the many variants that influence the infant in the critical hours before, during, and after birth that has been assembled. Its strength is mainly in the

ability of the contributors, all of whom are among the best in their respective fields, and in the limitation of their presentations to areas with which they are quite familiar, with little speculation in others. Each contributor has documented the facts as we know them, what to do with the facts about each case as it presents, and what to expect—with very little theorizing, particularly in areas of interest that are not their own. For this they are to be commended. The contributions from obstetricians are well made, and are pleasing also; the knowledge that pregnancy and delivery are successful only if the infant lives and does well is a concept that took too long to become fact.

The section on *Standard* Terminology that appears in Chapter One and an excellent Glossary are items that are absolute necessities for a publication of this type, and the contributors have been uniform in their references. The use of statistics is good—not overbearing, just informative. Each chapter has a comprehensive bibliography to itself which will make the book a very useful guide.

In summary, this is a well-written book that is well edited; terminology is defined from the beginning; the contributors are well chosen. The major criticism would be of geographical selection of contributors—others in other parts of the world are also working in this field. To quote from the preface, *The Concept that is advanced is total*—it is and it is well done.

DIE OEDEME. PHYSIOPATHOLOGIE UND THERAPIE DER SALZ- UND WASSERRETENTION. By Priv.-Doz. Dr. Jean Fabre, Geneva, with the cooperation of Dr. Andreas Fanconi and Dr. Martin Rothlin, with a foreword by Prof. Dr. Rene S. Mach, Geneva. Original in French; German translation by Dr. A. Fanconi and Dr. M. Rothlin. Basel, 1960, Benno Schwabe & Company, 304 pages. Price: cloth, Sw. Fr. 38. (Sole U.S. and Canadian representative: Intercontinental Medical Book Corp., 381 Fourth Ave., New York 16, N. Y.)

The authors' goal in this book is to survey and summarize the experimental and clinical findings in research on edema and salt and water metabolism and to draw pertinent physiologic, pathophysiologic, and therapeutic conclusions. The book is divided into three parts.

The first part gives a clear picture of the present knowledge of salt and water metabolism. The influence and importance of antidiuretic hormone, aldosterone, kidney function, and hemodynamic factors on salt and water metabolism and intracellular and extracellular fluid compartments are discussed.

The second part deals with the pathophysiology of the numerous types of edema of different pathogenesis, including cardiac, renal, hepatic, endocrine, iatrogenic, pregnancy, malnutrition, inflammatory, allergic, venous, and lymphatic edemas.

In the third part the therapeutic possibilities and problems are evaluated. The values of salt-free diet, cation exchange resins, usual diuretic agents, paracentesis, adrenal steroids, phlebotomy, and artificial dialysis are discussed. The aldosterone antagonists were not included.

The book adequately surveys many of the most recent areas in research on salt and water metabolism. The material is presented with clarity and in an easily understandable form. The book should be of value particularly to those who are interested in the problems of salt and water metabolism.

QUANTITATIVE VECTORELECTROCARDIOGRAPHY. By Louis Brinberg, M.D., Division of Cardiology, Department of Medicine, The Mount Sinai Hospital of New York. Baltimore, 1960, Waverly Press, Inc., 123 pages. Price $5.25.

This book represents a compilation of several articles published separately by the author. The chapter headings reveal the essential contents of the book: I. The Orthovectorcardiogram, A Record of Magnitude and Orientation of the Instantaneous Forces of the Cardiac Cycle. II. Spherical Vectorcardiography. The Use of a Sphere to Determine Angles, Planes, Rotation, Velocity and Tortuosity. III. The Electric Axis and Ventricular Gradient as Determined From the Twelve-Lead Electrocardiogram. IV. The QRS-T Angle as Determined From the Twelve-Lead Electrocardiogram. V. A Three-Dimensional Statistical Technique: Its Application to the Ventricular Gradient. VI. The Ventricular Gradient. VII. A Rapid Method of Determining Space-Polar Coordinates.

The book is profusely illustrated and should be helpful to anyone working in the field of vectorcardiography, particularly if he has had little or no formal training in analytic geometry.

The author tacitly assumes that the electrical forces generated by the heart can be represented as if they were produced by a single dipole, fixed in location. The justification for applying the precise quantitative methods described in this book to measurements based on such a dipole concept is questionable.

DER AKUTE ARTERIENVERSCHLUSS DER EXTREMITÄTEN (EMBOLIE — THROMBOSE — PSEUDOEMBOLIE). DIAGNOSE UND THERAPIE. By A. Kappert, Bern and Stuttgart, 1960, Hans Huber Verlag, 175 pages. Price: DM 34.

In spite of the relatively small size of this volume, it is a rather comprehensive text on acute occlusion of arteries in the extremities, including pathophysiology, etiology, clinical symptoms, diagnosis and therapy, with 631 bibliographical references. Acute arterial occlusion is of particular clinical interest because of the need for immediate therapy. Considerable space is devoted to drug therapy (anticoagulants, streptokinase, plasmin, activation of fibrinolysin). However, "statistical comparison between the

results of conservative and surgical treatment of peripheral emboli is difficult, and individual prognosis is not possible" (p. 69). Among the objective diagnostic methods, examples of continuous recording of skin temperature (Figs. 3 and 4) and of Gesenius' "double oscillography" (*Deutsche medizinische Wochenschrift* 74:1, 1949; Fig. 5), before and after surgical treatment, are given. The resulting improvement of peripheral circulation in these examples is dramatic. Winsor's segmental plethysmography (*Angiology* 8:87, 1957) and rheography (impedance plethysmography) are also recommended. Although peripheral arterial occlusion is the main topic, naturally the discussion of pathology, etiology, and therapy includes related aspects of heart disease, and thrombosis and embolization in other vascular regions. Of interest is the differentiation of "pseudoemboli" (acute spastic arterial occlusion) from true peripheral thrombosis or emboli (pp. 118-136). Collateral arteries in the extremities are shown in Figs. 16-20 (Appendix).

Announcements

The University of Colorado School of Medicine announces the COCHEMS COMPETITION, funds for which were provided in the will of the late Mrs. Jane Nugent Cochems. A prize of $2,500 will be awarded to the author of the best paper on the subject of "The Diagnosis, Etiology and Treatment of Thrombophlebitis." The competition is open to all physicians, and entries must be received, in triplicate, on or before Oct. 1, 1961.

The Colorado National Bank of Denver, Trustee under the will of Jane Nugent Cochems, has requested the Dean of the University of Colorado School of Medicine to conduct the competition. The judges, appointed by him, are Dr. Michael E. DeBakey, Professor and Head of the Department of Surgery, Baylor University College of Medicine, and Dr. Sol Sherry, Professor of Medicine, Washington University School of Medicine.

Papers submitted in the competition may not be published until after the winner of the competition has been announced. At that time, the winning paper and all others may be published at the discretion of individual authors. It should be noted, however, that those involved in conducting the competition will not assume any responsibility for submitting manuscripts for publication nor for any costs incident thereto. The winning paper, if published, must carry the designation, "Awarded the Jane Nugent Cochems Prize."

Questions regarding the competition and all manuscripts should be directed to Dr. Robert J. Glaser, Vice-President for Medical Affairs and Dean of the University of Colorado School of Medicine, University of Colorado Medical Center, 4200 East Ninth Avenue, Denver 20, Colo.

THE SUB-BOARD OF PEDIATRIC CARDIOLOGY of the American Board of Pediatrics announces that its organization is complete and that it is now ready to accept applications for certification, both on record and by examination. The former must be submitted by Dec. 31, 1961.

Applications for approval of residency training programs in pediatric cardiology will also be accepted.

Full information and application forms may be obtained from: The Executive Secretary, American Board of Pediatrics, 6 Cushman Road, Rosemont, Pa.

The members of the Sub-Board of Pediatric Cardiology are: James W. DuShane, Chairman, Rochester, Minn.; Forrest H. Adams, Los Angeles, Calif.; Edward C. Lambert, Buffalo, N. Y.; Alexander S. Nadas, Boston, Mass.; Saul J. Robinson, San Francisco, Calif.; and Helen B. Taussig, Baltimore, Md.

A COURSE IN ELECTROCARDIOGRAPHIC INTERPRETATION for *graduate physicians* will be given at the Michael Reese Hospital by Louis N. Katz, M.D., and Alfred Pick, M.D. (respectively, Director and Associate Director of the Cardiovascular Department), and Associates. The class will meet daily from 9:00 A.M. to 5:00 P.M., July 17 through July 29, 1961.

Further information and a copy of the lecture schedule may be obtained upon application to Miss Beverley Petzold, Secretary, Cardiovascular Department, Medical Research Institute, Michael Reese Hospital and Medical Center, Chicago 16, Ill.

The Fifth International Congress of THE INTERNATIONAL CARDIOVASCULAR SOCIETY will be held in Dublin, Ireland, at the University College, September 7-9, 1961.

For further information contact the Secretary-General, The International Cardiovascular Society, 715 Park Avenue, New York 21, N. Y.

THE AMERICAN COLLEGE OF CARDIOLOGY will hold its Tenth Anniversary Convention at the Biltmore Hotel, New York on May 17-20, 1961, according to an announcement by Gabriel F. Greco, M.D., Ozone Park, N. Y., Chairman, Public Relations Committee. William Bennett Bean, M.D., Iowa City, will deliver the Memorial Lecture in honor of Franz Groedel, M.D., Founder and first President of the College, in the Empire City, the birthplace of the College. The tenth President of the College, Dr. Louis F. Bishop, New York, will confer on Dr. Bean the Groedel Medal for 1961. George W. Calver, Washington, D.C., is Chairman, Convention Committee. J. Maxwell Chamberlain, M.D., New York, is in charge of local arrangements. George C. Griffith, M.D., Los Angeles, Calif., is the Chairman of the Scientific Program. The scientific sessions will feature symposia on the latest achievements in cardiology, and include, among many topics, problems in cardiovascular management, with relation to coronary and cerebral circulation, use of anticoagulants, fibrinolysins, monoamine oxidase inhibitors, digitalis, diuretics, surgery, with valve prostheses in aortic and mitral stenosis and insufficiency; instrumentation in surgery, isotope renogram, aorto-renal arteriogram, renal function tests; critical review of latest problems in congenital heart disease; and cardiac metabolism. There will be fireside conferences, exhibits, and a motion picture program.

For details, write to P. Reichert, M.D., Executive Secretary, American College of Cardiology, Empire State Bldg., New York, N. Y.

THE LIFE INSURANCE MEDICAL RESEARCH FUND has announced the appointment of William A. Jeffers, M.D., as Scientific Director. The appointment was effective as of April 15, 1961.

The new address for the offices of the Fund is: 1030 East Lancaster Ave., Rosemont, Pa.